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		E KRUSE L/AU
L1	112	S E3,E5,E12-E14
		E CHANG A/AU
L2	185	S E3,E5-E9
L3	22	S E118
		E DEHAVEN/AU
L4	16	S E9-E11
L5	48	S E15-E18
		E HUDKINS/AU
L6	1	S E4
		E GAUL F/AU
L7	16	S E3-E5
		E KUMAR V/AU
L8	772	S E3-E74
		E KUMAR VIRENDRA/AU
L9	95	S E3
L10	7	S E2
L11	1	S E5
		E MARELLA M/AU
L12	24	S E3,E5,E6
		E MAYCOCK A/AU
L13	64	S E3,E4,E6,E8,E9
		E ZHANG W/AU
L14	554	S E3,E22
		E ZHANG WEI/AU
L15	1248	S E3,E69
		E ZHANG WEIYUAN/AU
L16	23	S E3
L17	3122	S L1-L16
		E PRURIT/CW
L18	889	S E5,E6
		E ANTIPRURIT/CW
		E ITCH/CW
		E PRURIGO/CW
		E HYPERALG/CW
L19	327	S E4
		E PRURITIS/CT
		E E4+ALL
L20	890	S E5,E4+NT
		E HYPERALG/CT
		E E4+ALL
L21	1152	S E1,E2
		E PRURIT
L22	1629	S E5-E21
		E PRURIG
L23	74	S E4-E8
		E ITCH
L24	1292	S E3,E6,E9,E10,E15,E16,E17,E22
		E SCRATCH
L25	16643	S E3,E5,E10,E13-24
L26	8	S E24,E26,E34
L27	29	S E38
L28	1	S E37
		E ANTIITCH
L29	67	S E4
		E ANTIPRUR
L30	274	S E5-E12
L31	2	S E93
L32	1	S E103
		E ANTISCRATCH

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jan.delaval@uspto.gov

L33 129 S E3,E4,E5
E ANTIHYPERALG
L34 110 S E4-E6
L35 20532 S L18-L34
L36 2743 S KAPPA(L)RECEPTOR(L)AGONIST(L) (OPIOID? OR OPIAT?)
L37 4877 S KAPPA(L)RECEPTOR(L) (OPIOID? OR OPIAT?)
L38 31 S L35 AND L36
L39 46 S L35 AND L37
L40 115 S (OPIOID? OR OPIAT?) (L)AGONIST AND L35
L41 235 S (OPIOID? OR OPIAT?) (L)RECEPTOR AND L35
L42 57 S (OPIOID? OR OPIAT?) (L)KAPPA AND L35
L43 57 S L38,L39;L42
L44 200 S L40,L41 NOT L43
L45 41 S KAPPA(L)AGONIST AND L35
L46 58 S L43,L45
L47 200 S L40,L41 NOT L46
L48 5 S L17 AND L46
L49 1 S L17 AND L47
L50 6 S L48,L49
E ADOLOR/PA,CS
L51 30 S E3-E14
L52 14 S L51 AND L35
L53 9 S L51 AND L36,L37
L54 17 S L51 AND (OPIOID? OR OPIAT?) (L) (AGONIST OR RECEPTOR OR KAPPA
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L56 7 S L53,L54 AND L52
L57 7 S L50,L56
L58 17 S L52-L55 NOT L57
L59 251 S L46,L47 NOT L57,L58
L60 110 S L59 AND (PY<=1996 OR PRY<=1996 OR AY<=1996)
L61 18 S L60 AND (PERIPHERAL OPIATE RECEPTOR OR ANTIPRUR? OR SCRATCHIN
L62 42 S L57,L58,L61
L63 16 S L60 AND PRURITUS/CW,BI
L64 50 S L62,L63

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FILE LAST UPDATED: 16 Jan 2002 (20020116/ED)

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L64 ANSWER 1 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 2002:2292 HCAPLUS
 TI Alvimopan* (ADL 8-2698) Is a Novel Peripheral Opioid Antagonist
 AU Schmidt, William K.
 CS Adolor Corporation, Exton, PA, 19341-1127, USA
 SO American Journal of Surgery (2001), 182(5A), 27S-38S
 CODEN: AJSUAB; ISSN: 0002-9610
 PB Excerpta Medica, Inc.
 DT Journal
 LA English
 AB Alvimopan (ADL 8-2698; Adolor Corporation, Exton, PA, USA) is a novel, peripherally restricted **opioid** antagonist. After oral administration, it has activity specific to the gastrointestinal (GI) tract. ADL 8-2698 has low systemic absorption and a high affinity for **.mu.-opioid receptors**. In healthy subjects, ADL 8-2698 antagonized loperamide-induced changes in GI transit and prevented morphine-induced delays in oral-cecal transit time without antagonizing centrally mediated **opioid** effects, such as analgesia or pupillary constriction. In the treatment of **opioid** naive patients who underwent surgery and received **opioids** for acute pain, oral ADL 8-2698 (6.0 mg) improved the management of postoperative ileus (POI) by shortening the time to achieve normal bowel function and, ultimately, hospital stay. Postoperative nausea and vomiting and the overall incidence of all GI side effects were reduced in patients treated with ADL 8-2698 for POI. Analgesia was not compromised, because there were no changes in median **opioid** consumption or Visual Analog Scale (VAS) pain scores in patients treated with ADL 8-2698 vs. patients treated with placebo. No drug-related side effects were obsd. in acute pain postsurgical patients in the initial POI study. In patients treated with **opioids** for chronic pain or **opioid** addiction, lower doses of oral ADL 8-2698 (0.5 to 3.0 mg) reversed **opioid** bowel dysfunction (OBD) and normalized GI activity. These effects were evident without compromising **opioid** analgesia or inducing central nervous system symptoms of withdrawal. Some chronic **opioid** patients receiving apparently supramaximal doses of ADL 8-2698 (.gtoreq.3.0 mg) reported localized GI side effects, possibly indicative of a localized GI withdrawal response. The most common side effects of ADL 8-2698 in chronic pain patients with OBD were abdominal pain, flatulence, and diarrhea. These effects were not obsd. in most OBD patients receiving lower doses of ADL 8-2698. Overall, ADL 8-2698 was well tolerated in clin. trials. Further studies to evaluate the efficacy and safety of ADL 8-2698 in clin. practice are in progress.

L64 ANSWER 2 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 2001:833071 HCAPLUS
 DN 135:352822
 TI **Opioid agonist** and antagonist compositions and methods for enhancing potency or reducing adverse side effects of **opioid agonists**
 IN Sherman, Barry; Remien, Mary; Barbier, Remi; Dumas, Kathleen; Schoenhard, Grant
 PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of Yeshiva University
 SO PCT Int. Appl., 835 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001085150	A2	20011115	WO 2001-US14644	20010504
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,				

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 HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
 LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
 RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,
 VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
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 BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
 US 6011004 A 20000104 US 1996-768221 19961217 <--
 AU 9947399 A1 19991028 AU 1999-47399 19990906 <--
 WO 2000067739 A2 20001116 WO 2000-US12493 20000505
 WO 2000067739 A3 20010125

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR,
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 SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
 ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
 DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
 CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 2000-202227 P 20000505
 US 2000-202268 P 20000505
 US 2000-566071 A 20000505
 WO 2000-US12493 W 20000505
 US 2000-244482 P 20001030
 US 2000-245110 P 20001101
 US 2000-246235 P 20001102
 US 2001-756331 A 20010108
 US 1990-612847 B1 19901113 <--
 US 1993-153796 A1 19931117 <--
 AU 1995-32769 A3 19950718 <--
 US 1999-306164 A2 19990506

AB The invention provides compns. and methods using an **opioid**
agonist and an **opioid** antagonist to differentially dose
 a human subject so as to either enhance analgesic potency without
 attenuating an adverse side effect of the **agonist**, or
 alternatively maintain the analgesic potency of the **agonist**
 while attenuating an adverse side effect of the **agonist**. The
 invention addnl. relates to novel **opioid** compns. and methods for
 the gender-based dosing of men and women.

L64 ANSWER 3 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2001:757813 HCAPLUS

DN 135:318517

TI Preparation of 1-aralkanoyl-2-pyrrolidinomethylpiperazines and analogs as
.kappa.-opioid receptor agonists

IN Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar,
 Virendra; Gaul, Forrest; Chang, An-Chih; Guo, Deqi

PA Adolor Corporation, USA

SO U.S., 115 pp., Cont.-in-part of U.S. 5,945,443.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6303611	B1	20011016	US 1998-150369	19980909
	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 6057323	A	20000502	US 1998-183011	19981030
	US 6054445	A	20000425	US 1999-307387	19990507
	WO 2000014065	A1	20000316	WO 1999-US13680	19990616

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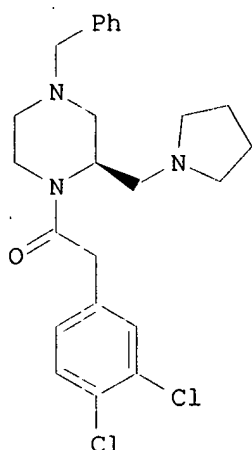
GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO,
RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
PT, SE

AU 9944428 A1 20000327 AU 1999-44428 19990616
EP 1112252 A1 20010704 EP 1999-927550 19990616

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, FI

US 6239154 B1 20010529 US 1999-372191 19990811
PRAI US 1996-612680 A1 19960308
US 1997-796078 A3 19970205
US 1997-899086 A3 19970723
US 1998-34661 A2 19980303
US 1998-150369 A2 19980909
US 1998-183011 A3 19981030
WO 1999-US13680 W 19990616

GI



I

AB Title compds., e.g., I, were prepd. Data for biol. activity of title
compds. were given.

RE.CNT 17

RE

- (1) Anon; EP 0147085 1984 HCAPLUS
- (3) Anon; EP 0233793 1987 HCAPLUS
- (4) Anon; EP 0330461 1989 HCAPLUS
- (5) Anon; EP 0330467 1989 HCAPLUS
- (6) Anon; EP 0366327 1989 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 4 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2001:434812 HCAPLUS

DN 135:29160

TI Methods using peripheral .mu. opioid antagonists for the treatment and
prevention of dizziness and pruritus

IN Carpenter, Randall L.

PA Adolor Corporation, USA

SO PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001041705	A2	20010614	WO 2000-US42310	20001129

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HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

AU 2001041369 A5 20010618 AU 2001-41369 20001129
PRAI US 1999-450812 A 19991129
WO 2000-US42310 W 20001129

OS MARPAT 135:29160

AB Methods are provided for the treatment and/or prevention of dizziness and/or **pruritus**. The methods may comprise administering to a patient an effective amt. of a peripheral .mu. opioid antagonist compd. Preferred compds. for use in the methods include piperidine-N-alkylcarboxylates, quaternary morphinans, opium alkaloid derivs. and quaternary benzomorphans. The methods are particularly suitable for treating and/or preventing dizziness and/or **pruritus** assocd. with opioid compds.

L64 ANSWER 5 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2001:392068 HCAPLUS

DN 135:5628

TI Preparation of 1-acyl-2-pyrrolidinylmethylpiperazines and related compounds as .kappa. agonists.

IN Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar, Virendra; Gaul, Forrest; Guo, Deqi

PA Adolor Corporation, USA

SO U.S., 119 pp., Cont.-in-part of U.S. Ser. No. 150,369.

CODEN: USXXAM

DT Patent

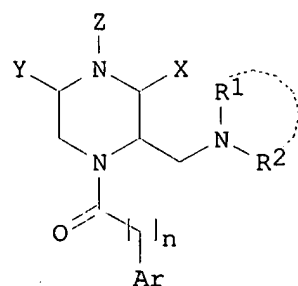
LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6239154	B1	20010529	US 1999-372191	19990811
	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 6303611	B1	20011016	US 1998-150369	19980909
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A3	19970205		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	US 1998-150369	A2	19980909		

OS MARPAT 135:5628

GI



I

AB Title compds., e.g., [I; n = 1-3; R1, R2 = Me, (CH2)m, CH2CH(OH)(CH2)2;

CH₂CHF(CH₂)₂, etc.; m = 4-8; Ar = (substituted) Ph, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, 9-fluorenyl; Z = PO₃H₂, (CH₂)_pCO₂H, SO₂Me, SO₂NH₂, tetrazolylmethyl, etc.; p = 0-20; X, Y = CH₂NHSO₂Me, CH₂NHPO₃H₂, (CH₂)_qO(CH₂)_qSO₃H, etc.; q = 1-20], were prepd. Thus, Me (R,S)-4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate hydrochloride (prepn. outlined) at 300 mg gave 98% inhibition of formalin-induced nociception in rat paws.

RE.CNT 2

RE

- (1) Kruse; US 5688955 1997 HCAPLUS
- (2) Kruse; US 5945443 1999 HCAPLUS

L64 ANSWER 6 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:844938 HCAPLUS

DN 134:115816

TI Arylacetamides as peripherally restricted **kappa opioid receptor agonists**

AU Kumar, Virendra; Marella, Michael A.; Cortes-Burgos, Luz; Chang, An-Chih; Cassel, Joel A.; Daubert, Jeffrey D.; DeHaven, Robert N.; DeHaven-Hudkins, Diane L.; Gottshall, Susan L.; Mansson, Erik; Maycock, Alan L.

CS Adolor Corporation, Malvern, PA, 19355, USA

SO Bioorg. Med. Chem. Lett. (2000), 10(22), 2567-2570

CODEN: BMCLE8; ISSN: 0960-894X

PB Elsevier Science Ltd.

DT Journal

LA English

AB Analogs of the **.kappa.-opioid receptor agonist**, ICI 199441, were prepd. Ki values for these analogs at the cloned human **.kappa. opioid receptor** ranged from 0.058 to 25 nM. Trifluoromethylaryl derivs. were potent analgesics when administered s.c. in the rat and were more peripherally restricted than the parent compd., ICI 199441.

RE.CNT 12

RE

- (1) Barber, A; Exp Opin Invest Drugs 1997, V6, P1351 HCAPLUS
- (2) Barlow, J; J Med Chem 1991, V34, P3149 HCAPLUS
- (3) Chang, A; J Med Chem 1994, V37, P4490 HCAPLUS
- (4) Costello, G; Eur J Pharm 1988, V151, P475 HCAPLUS
- (5) Costello, G; J Med Chem 1991, V34, P181 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 7 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:814295 HCAPLUS

DN 133:329619

TI Compositions and methods using an opioid antagonist for enhancing analgesic potency of tramadol and attenuating its adverse side effects

IN Crain, Stanley M.; Shen, Ke-Fei; Sherman, Barry; Remien, Mary; Barbier, Remi; Friedmann, Nadav

PA Pain Therapeutics, Inc., USA; Albert Einstein College of Medicine of Yeshiva University

SO PCT Int. Appl., 114 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 12

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000067739	A2	20001116	WO 2000-US12493	20000505
	WO 2000067739	A3	20010125		

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US 6011004 A 20000104 US 1996-768221 19961217 <--
US 2001006967 A1 20010705 US 1999-306164 19990506 <--
AU 9947399 A1 19991028 AU 1999-47399 19990906 <--
WO 2001085257 A2 20011115 WO 2001-US14377 20010504

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WO 2001085150 A2 20011115 WO 2001-US14644 20010504

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BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-306164 A2 19990506
US 1990-612847 B1 19901113 <--
US 1992-947690 B2 19920921 <--
US 1993-97460 A2 19930727 <--
US 1993-153796 A1 19931117 <--
US 1994-276966 A2 19940719 <--
AU 1995-32769 A3 19950718 <--
US 1996-759590 A1 19961203 <--
US 1998-94977 A2 19980616
US 2000-202227 P 20000505
US 2000-202268 P 20000505
US 2000-566071 A 20000505
WO 2000-US12493 W 20000505
US 2000-244482 P 20001030
US 2000-245110 P 20001101
US 2000-246235 P 20001102
US 2001-756331 A 20010108

AB The invention provides compns. and methods with tramadol and an
opioid antagonist to enhance analgesic potency and/or attenuate
one or more adverse effects of tramadol, including adverse side effect(s)
in humans such as nausea, vomiting, dizziness, headache, sedation
(somnolence) or **pruritis**. Compns. and methods are provided for
selectively enhancing the analgesic potency of tramadol and simultaneously
attenuating anti-analgesia, hyperalgesia, hyperexcitability, phys.
dependence and/or tolerance effects assocd. with the administration of
tramadol. The methods of the invention comprise administering to a
subject an analgesic or subanalgesic amt. of tramadol and an amt. of
excitatory **opioid receptor** antagonist, e.g. naltrexone
or nalmefene, effective to enhance the analgesic potency of tramadol and
attenuate the anti-analgesia, hyperalgesia, hyperexcitability, phys.
dependence and/or tolerance effects of tramadol.

L64 ANSWER 8 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:331874 HCAPLUS

TI Synthesis and evaluation of novel peripheral .kappa.
opioid receptor agonists.

AU Guo, Deqi; Kumar, Virendra; Maycock, Alan; DeHaven, Robert N.; Daubert,
Jeff D.; Cassel, Joel A.; Gauntner, Erin K.; DeHaven-Hudkins, Diane L.;
Gottshall, Susan L.; Greiner, Susan; Koblish, Mike; Little, Pat J.

CS Adolor Corporation, Malvern, PA, 19355, USA

SO Book of Abstracts, 219th ACS National Meeting, San Francisco, CA, March

26-30, 2000 (2000), MEDI-263 Publisher: American Chemical Society,
Washington, D. C.
CODEN: 69CLAC

DT Conference; Meeting Abstract

LA English

AB Although centrally active **.kappa. agonists** have analgesic properties, they have been of limited therapeutic use because of side effects such as sedation, dysphoria and diuresis. Recent evidence indicates that the **opioid antinociception** can also be mediated by activation of **opioid receptors** located outside the CNS. One of the goals at Adolor is to modify centrally active **.kappa. agonists** to reduce CNS penetration, thus eliminating or minimizing the side effects. We have recently reported 2-(4-trifluoromethylphenyl)-N-methyl-N-[1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide 1 as a highly potent **.kappa. agonist** with a profile of peripheral selectivity better than that of centrally active ICI 199441 (2). To improve the peripheral selectivity of 1, we have synthesized a series of analogs of general structure 3 modified in the central Ph ring and evaluated them for in vitro binding affinity, in vivo antinociceptive activity, and peripheral selectivity. The synthetic strategy and the results from the biol. studies will be presented.

L64 ANSWER 9 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:284003 HCAPLUS

DN 132:293778

TI Preparation of 1-acyl-2-pyrrolidinylmethylpiperazines and related compounds as **.kappa. agonists**.

IN Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar, Virendra; Gaul, Forrest; Chang, An-chih; Guo, Deqi

PA Adolor Corporation, USA

SO U.S., 121 pp., Cont.-in-part of U.S. Ser. No. 150,369.

CODEN: USXXAM

DT Patent

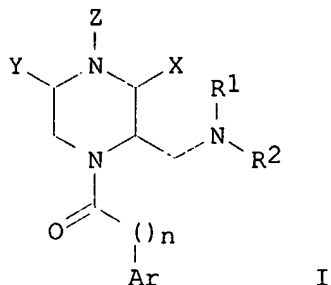
LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6057323	A	20000502	US 1998-183011	19981030
	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 6303611	B1	20011016	US 1998-150369	19980909
	US 6054445	A	20000425	US 1999-307387	19990507
PRAI	US 1996-612680	A1	19960308		
	US 1997-796078	A3	19970205		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	US 1998-150369	A2	19980909		
	US 1998-183011	A3	19981030		

OS MARPAT 132:293778

GI



AB Title compds., e.g., [I; n = 1-3; R1, R2 = Me, (CH2)m, CH2CH(OH)(CH2)2; CH2CHF(CH2)2, etc.; m = 4-8; Ar = (substituted) Ph, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, 9-fluorenyl; Z = PO3H2, (CH2)pCO2H, SO2Me, SO2NH2, tetrazolylmethyl, etc.; p = 0-20; X, Y = CH2NHSO2Me, CH2NHPO3H2, (CH2)qO(CH2)qSO3H, etc.; q = 1-20], were prepd. as analgesics and anti-pruritic agents. Thus, Me (R,S)-4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate hydrochloride (prepn. outlined) at 300 mg gave 98% inhibition of formalin-induced nociception in rat paws.

RE.CNT 26

RE

(1) Anon; EP 0147085 1984 HCAPLUS

(2) Anon; EP 0207773 1986 HCAPLUS

(3) Anon; EP 0233793 1987 HCAPLUS

(4) Anon; EP 0330461 1989 HCAPLUS

(5) Anon; EP 0330467 1989 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 10 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:260010 HCAPLUS

DN 132:298831

TI Peripherally acting anti-pruritic opiates

IN Farrar, John J.; Cowan, Alan

PA Adolor Corporation, USA

SO PCT Int. Appl.; 47 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000021530	A1	20000420	WO 1999-US17439	19990802
	W: AL, AU, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KR, LC, LK, LR, LV, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9952500	A1	20000501	AU 1999-52500	19990802
	EP 1119354	A1	20010801	EP 1999-937727	19990802
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LV, FI, RO				
	BR 9914380	A	20010807	BR 1999-14380	19990802
PRAI	US 1998-168724	A	19981009		
	WO 1999-US17439	W	19990802		

OS MARPAT 132:298831

AB Anti-pruritic compns. for the prevention or treatment of pruritus comprise e.g., morpholines, piperidines, oxadiazoles, phenylamidinoureas, and 1-azabicyclo[2.2.2]octanes. Thus, rectal suppositories contained loperamide 80, propylene glycol 95, and PEG-4000 1800 g. Loperamide at 2.5 mg/kg antagonized Compd. 48/80-induced scratching in a dose-dependent manner, as demonstrated in mice.

RE.CNT 3

RE

- (1) Diamond; US 4203920 A 1980 HCAPLUS
- (2) Park; US 5242944 A 1993 HCAPLUS
- (3) Wals; US 4824853 A 1989 HCAPLUS

L64 ANSWER 11 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 2000:175792 HCAPLUS

DN 132:222550

TI Preparation of 1-acyl-2-pyrrolidinylmethylpiperazines and related compounds as **.kappa. agonists**.

IN Zhang, Wei Yuan; Maycock, Alan L.; Marella, Michael Anthony; Kumar, Virendra; Gaul, Forrest; Chang, An-chih; Guo, Deqi

PA Adolor Corp., USA

SO PCT Int. Appl., 216 pp.

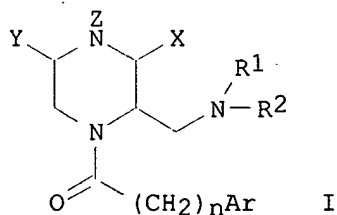
CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000014065	A1	20000316	WO 1999-US13680	19990616
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW				
	RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	US 6303611	B1	20011016	US 1998-150369	19980909
	AU 9944428	A1	20000327	AU 1999-44428	19990616
	EP 1112252	A1	20010704	EP 1999-927550	19990616
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
PRAI	US 1998-150369	A	19980909		
	US 1996-612680	A1	19960308		
	US 1997-796078	A3	19970205		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	WO 1999-US13680	W	19990616		
OS	MARPAT 132:222550				
GI					



AB Title compds., e.g., [I; n = 1-3; R1, R2 = Me, (CH2)m, CH2CH(OH)(CH2)2; CH2CHF(CH2)2, etc.; m = 4-8; Ar = (substituted) Ph, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, 9-fluorenyl; Z = PO3H2, (CH2)pCO2H, SO2Me, SO2NH2, tetrazolylmethyl, etc.; p = 0-20; X, Y = CH2NH2SO2Me, CH2NHPO3H2, (CH2)qO(CH2)qSO3H, etc.; q = 1-20], were prepd. Thus, Me (R,S)-4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate hydrochloride (prepn. outlined) at 300 mg gave 98% inhibition of formalin-induced nociception in rat paws.

RE.CNT 1

RE

- (1) Lednicer; US 4065573 A 1977 HCAPLUS

L64 ANSWER 12 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1999:617474 HCAPLUS
TI Synthesis and chiral separation of the four diastereomers of GR 94839.
AU Gaul, Forrest E.; Zhang, Wei-Yuan; Maycock, Alan L.; DeHaven, Robert N.;
Daubert, Jeffrey D.; Cassel, Joel A.; Mansson, Eric; Geiser, Fiona; Lee,
James; Champion, William L., Jr.
CS Medicinal Chemistry, Adolor Corporation, Malvern, PA, 19355, USA
SO Book of Abstracts, 218th ACS National Meeting, New Orleans, Aug. 22-26
(1999), MEDI-102 Publisher: American Chemical Society, Washington, D. C.
CODEN: 67ZJA5
DT Conference; Meeting Abstract
LA English
AB There is evidence that **kappa** (k) **agonists** with limited
access to the central nervous system could be antinociceptive while
lacking the side effects, such as sedation and dysphoria, produced by
centrally active **k agonists**. GR 94839 (a mixt. of
diastereomers), a **k opioid agonist** with limited access
to the central nervous system, has been reported to be a potent analgesic
in animals. As part of our peripheral **kappa** program, we have
used GR 94839 as a template for structure modifications to improve **k**
receptor binding and peripheral selectivity. One goal was to
compare the **opioid receptor** binding activity of the
four diastereomers of GR 94839 (). In our hands the reported chiral
routes to these diastereomers yielded &#pound; 40 %. The two racemic
routes followed by chiral sepn. using a preparative CHIRALPAK AD column
yielded all four diastereomers in high. The binding affinities of the
diastereomers to m, d, and **k opioid receptors** will be
presented.

L64 ANSWER 13 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1999:226280 HCAPLUS
DN 131:39586
TI Loperamide (ADL 2-1294), an opioid **antihyperalgesic** agent with
peripheral selectivity
AU DeHaven-Hudkins, D. L.; Burgos, L. Cortes; Cassel, J. A.;
Daubert, J. D.; DeHaven, R. N.; Mansson, E.; Nagasaka, H.; Yu, G.; Yaksh,
T.
CS Adolor Corporation, Malvern, PA, USA
SO J. Pharmacol. Exp. Ther. (1999), 289(1), 494-502
CODEN: JPETAB; ISSN: 0022-3565
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB The **antihyperalgesic** properties of the **opiate**
antidiarrheal agent loperamide (ADL 2-1294) were investigated in a variety
of inflammatory pain models in rodents. Loperamide exhibited potent
affinity and selectivity for the cloned μ . (K_i = 3 nM) compared with the
 δ . (K_i = 48 nM) and **.kappa**. (K_i = 1156 nM) human
opioid receptors. Loperamide potently stimulated
[35S]guanosine-5'-O-(3-thio)-phosphate binding (EC_{50} = 56 nM), and
inhibited forskolin-stimulated cAMP accumulation (IC_{50} = 25 nM) in Chinese
hamster ovary cells transfected with the human μ . **opioid**
receptor. The injection of 0.3 mg of loperamide into the
intra-articular space of the inflamed rat knee joint resulted in potent
antinociception to knee compression that was antagonized by naloxone,
whereas injection into the contralateral knee joint or via the i.m. route
failed to inhibit compression-induced changes in blood pressure.
Loperamide potently inhibited late-phase formalin-induced flinching after
intrapaw injection (A_{50} = 6 μ .g) but was ineffective against early-phase
flinching or after injection into the paw contralateral to the
formalin-treated paw. Local injection of loperamide also produced
antinociception against Freund's adjuvant- (ED_{50} = 21 μ .g) or tape
stripping- (ED_{50} = 71 μ .g) induced hyperalgesia as demonstrated by
increased paw pressure thresholds in the inflamed paw. In all animal
models examd., the potency of loperamide after local administration was
comparable to or better than that of morphine. Loperamide has potential
therapeutic use as a peripherally selective **opiate**

antihyperalgesic agent that lacks many of the side effects
generally assocd. with administration of centrally acting **opiates**

RE.CNT 41

RE

- (1) Antonijevic, I; J Neurosci 1995, V15, P165 HCAPLUS
- (2) Bare, L; FEBS Lett 1994, V354, P213 HCAPLUS
- (3) Bianchi, C; Arzneim-Forsch/Drug Res 1977, V27, P1040 HCAPLUS
- (4) Blake, A; J Biol Chem 1997, V272, P782 HCAPLUS
- (5) Cabot, P; J Clin Invest 1997, V100, P142 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 14 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1999:212693 HCAPLUS

DN 130:257341

TI Film-forming compositions of **antihyperalgesic** opiates and method
of treating hyperalgesic and **pruritic** conditions therewith

IN Farrar, John J.; Maycock, Alan L.; Kumar, Virendra; Balogh, Imre Jim

PA Adolor Corporation, USA

SO U.S., 13 pp., Cont.-in-part of U.S. 5,667,773.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5888494	A	19990330	US 1997-891924	19970714
	US 5667773	A	19970916	US 1996-614027	19960312
	WO 9903455	A1	19990128	WO 1998-US12834	19980619
	W:		AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM		
	RW:		GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG		
	AU 9880749	A1	19990210	AU 1998-80749	19980619
	AU 728538	B2	20010111		
	EP 1003489	A1	20000531	EP 1998-929109	19980619
	R:		AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI		
	JP 2001510152	T2	20010731	JP 2000-502756	19980619
	NO 9906351	A	20000310	NO 1999-6351	19991220
PRAI	US 1996-614027	A2	19960312		
	US 1997-891924	A	19970714		
	WO 1998-US12834	W	19980619		
AB	Disclosed are topical film-forming compns. for the prevention and treatment of pruritus contg. (1) an opiate that is substantially devoid of central nervous system effects, (2) a film-forming polymeric material, and (3) an aq. pharmaceutically acceptable carrier. An emulsion contained loperamide.cntdot.HCl 30, ethanol 20, Na Et cellulose sulfate 25, Ca lactate 10, and water q.s. to 100 %.				

RE.CNT 28

RE

- (2) Anon; GB 933668 1963 HCAPLUS
- (3) Anon; DE 2636559 1977 HCAPLUS
- (7) Bernstein; Journal of Investigative Dermatology 1982, V78, P82 HCAPLUS
- (8) Calvet; US 5236947 1993 HCAPLUS
- (9) Clemente; US 5576346 1996 HCAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 15 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1999:77462 HCAPLUS

DN 130:158399

TI Film-forming compositions of **antihyperalgesic** opiates and method
of treating hyperalgesic and **pruritic** conditions therewith

IN Farrar, John J.; Maycock, Alan L.; Kumar, Virendra; Balogh, Imre
 PA Adolor Corporation, USA
 SO PCT Int. Appl., 37 pp.
 CODEN: PIXXD2
 DT Patent
 LA English
 FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9903455	A1	19990128	WO 1998-US12834	19980619
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	US 5888494	A	19990330	US 1997-891924	19970714
	AU 9880749	A1	19990210	AU 1998-80749	19980619
	AU 728538	B2	20010111		
	EP 1003489	A1	20000531	EP 1998-929109	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 2001510152	T2	20010731	JP 2000-502756	19980619
	NO 9906351	A	20000310	NO 1999-6351	19991220
PRAI	US 1997-891924	A	19970714		
	US 1996-614027	A2	19960312		
	WO 1998-US12834	W	19980619		
AB	Disclosed are topical film-forming compns. for the prevention and treatment of pruritus contg. an opiate that is substantially devoid of central nervous system effects. A topical prepn. contained loperamide.cntdot.HCl 25, Na carrageenan 25, Ca lactate 32, and water to 100 %.				

RE.CNT 3

- RE
 (1) Blank, I; 26 36559DT A1 1977
 (2) Clemente; US 5576346 A 1996 HCAPLUS
 (3) Tunc; US 4623539 A 1986 HCAPLUS

L64 ANSWER 16 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:816107 HCAPLUS

DN 130:47476

TI Peripherally acting anti-pruritic opiates

IN Farrar, John J.; Cowan, Alan

PA Adolor Corporation, USA

SO U.S., 15 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5849762	A	19981215	US 1997-892194	19970714
	WO 9903472	A1	19990128	WO 1998-US12831	19980619
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9878395	A1	19990210	AU 1998-78395	19980619
	AU 725444	B2	20001012		
	EP 1019051	A1	20000719	EP 1998-926595	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

BR 9810710 A 20000808 BR 1998-10710 19980619
 JP 2001510157 T2 20010731 JP 2000-502771 19980619
 ZA 9806207 A 19990126 ZA 1998-6207 19980713
 NO 9906354 A 20000308 NO 1999-6354 19991220
 PRAI US 1997-892194 A 19970714
 WO 1998-US12831 W 19980619
 OS MARPAT 130:47476
 AB Anti-**pruritic** compns. and methods of using the compns. for the prevention or treatment of **pruritus** comprising opiates in a pharmaceutically acceptable carrier. The mean anti-**pruritic** activity of 1-[3,3-diphenyl-3-(2-pyridyl)propyl]-4-phenyl-4-piperidinecarboxylic acid hydrochloride at 10.0 mg/kg s.c. in rats was 83%. Formulation of different pharmaceutical dosage forms are also disclosed.

RE.CNT 34

RE

(1) Adelstein; US 4066654 1978 HCAPLUS
 (2) Adelstein; US 4069223 1978 HCAPLUS
 (3) Adelstein; US 4072686 1978 HCAPLUS
 (5) Adelstein; US 4116963 1978 HCAPLUS
 (6) Adelstein; US 4194045 1980 HCAPLUS
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

L64 ANSWER 17 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:613444 HCAPLUS

DN 129:265466

TI Spray formulations of **antihyperalgesic** opiates and method of treating topical hyperalgesic conditions therewith

IN Maycock, Alan L.; Chang, An-chih; Farrar, John J.; Balogh, Imre

PA **Adolor Corp., USA**

SO U.S., 8 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5811078	A	19980922	US 1997-818559	19970314
	US 5798093	A	19980825	US 1997-892389	19970714
PRAI	US 1997-818559	A2	19970314		

OS MARPAT 129:265466

AB Spray formulations of anti-hyperalgesic opiates comprise an anti-hyperalgesic opiate having a peripheral selectivity of 251 to 1,280 in an aq. alc. mixt. contg. up to 15% ethanol, propanol, and/or isopropanol. Thus, 100 g of 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl-.alpha.,.alpha.-diphenyl-1-piperidinebutyramide was dissolved in 2 L of a 5 % ethanol/95 % water mixt. with agitation and the soln. was transferred to a pump action spray bottle.

L64 ANSWER 18 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:572232 HCAPLUS

DN 129:221192

TI Spray formulations of **antihyperalgesic** opiates for treatment of **pruritus**

IN Farrar, John J.; Chang, An-chih; Maycock, Alan L.; Balogh, Imre

PA **Adolor Corp., USA**

SO U.S., 9 pp. Cont.-in-part of U.S. Ser. No. 818,559.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5798093	A	19980825	US 1997-892389	19970714
	US 5811078	A	19980922	US 1997-818559	19970314
	WO 9903457	A1	19990128	WO 1998-US12832	19980619

W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9880748 A1 19990210 AU 1998-80748 19980619

AU 724727 B2 20000928

EP 1011647 A1 20000628 EP 1998-929108 19980619

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI

BR 9810711 A 20000808 BR 1998-10711 19980619

JP 2001510153 T2 20010731 JP 2000-502758 19980619

NO 9906234 A 20000310 NO 1999-6234 19991216

PRAI US 1997-818559 A2 19970314

US 1997-892389 A 19970714

WO 1998-US12832 W 19980619

OS MARPAT 129:221192

AB Spray formulations of anti-pruritic opiates having a peripheral selectivity of 251 to 1280 in a solvent mixt. of up to 15% alc. selected from the group consisting of EtOH, PrOH and iso-PrOH and water .gtoreq.85%. Thus, loperamide was prepd. by the reaction of 4-(p-chlorophenyl)-4-piperidinol with dimethyl(tetrahydro-3,3-diphenyl-2-furylidene)ammonium bromide in the presence of Na2CO3 and KI in 4-methyl-2-pentanone soln. Thus, 100 loperamide was dissolved in 2 L of EtOH-water (5:95) to form a spray.

L64 ANSWER 19 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:529782 HCAPLUS

TI Modified piperazine derivatives as peripherally selective **kappa opioid** analgesics

AU Zhang, Y.; Cassel, J.; Cortes-Burgos, L.; Daubert, J.; DeHaven, R.; DeHaven-Hudkins, D.; Gaul, F.; Gottshall, S.; Greiner, S.; Koblish, M.; Maycock, A.; Little, P.

CS Adolor Corporation, Malvern, PA, 19355, USA

SO Book of Abstracts, 216th ACS National Meeting, Boston, August 23-27 (1998), MEDI-297 Publisher: American Chemical Society, Washington, D. C. CODEN: 66KYA2

DT Conference; Meeting Abstract

LA English

AB There has been great interest by the pharmaceutical industry in the development of peripherally selective novel analgesics which act by activation of **.kappa.-opioid receptors**. **kappa. agonists** posses advantage over **.mu. agonists** being devoid of side effects such as respiratory depression, constipation and phys. dependence. Modification on the known centrally active **.kappa. agonist** (1, GR 89696) gave a series of new compds. (2) with improved peripheral selectivity. The synthesis, SAR and in vivo data will be presented.

L64 ANSWER 20 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:397785 HCAPLUS

DN 129:67799

TI Preparation of 1,4-diacyl-2-(pyrrolidinomethyl)piperazines and analogs as **kappa opioid receptor agonists**

IN Kruse, Lawrence I.; Chang, An-Chih; DeHaven-Hudkins, Diane L.; Farrar, John J.; Gaul, Forrest ; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan

PA Adolor Corp., USA

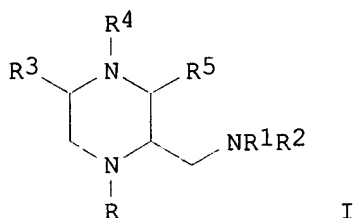
SO U.S., 67 pp., Cont.-in-part of U. S. 5,688,955. CODEN: USXXAM

DT Patent

LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5763445	A	19980609	US 1997-891833	19970714
	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	US 5981513	A	19991109	US 1998-45522	19980321
	WO 9903468	A1	19990128	WO 1998-US12769	19980619
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9879801	A1	19990210	AU 1998-79801	19980619
	AU 725232	B2	20001012		
	EP 998281	A1	20000510	EP 1998-930400	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9810712	A	20000905	BR 1998-10712	19980619
	JP 2001510154	T2	20010731	JP 2000-502767	19980619
	ZA 9806208	A	19990125	ZA 1998-6208	19980713
	US 6028063	A	20000222	US 1999-307517	19990507
	US 6180623	B1	20010130	US 1999-436057	19991108
	NO 9906352	A	20000313	NO 1999-6352	19991220
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A2	19970205		
	US 1997-891833	A3	19970714		
	US 1998-45522	A3	19980321		
	WO 1998-US12769	W	19980619		
	US 1999-307517	A3	19990507		
OS	MARPAT 129:67799				
GI					



AB Title compds. [I; R = CO(CH₂)_nR₆; R₁, R₂ = Me; R₁R₂ = (CH₂)_m, CH₂CH(OH)CH₂, CH₂CH₂OCH₂CH₂, etc.; R₃, R₅ = CH₂NHSO₂Me, CH₂NHP(O)(OH)₂, CH₂OP(O)(OH)₂, etc.; R₄ = P(O)(OH)₂, (CH₂)_pCO₂H, CO₂Me, etc.; R₆ = (un)substituted (hetero)aryl; m = 4-8; n = 1-3; p = 0-20] were prepd. for treatment of **pruritus**. Thus, (R)-I (R = COCH₂C₆H₃Cl₂-3,4, NR₁R₂ = pyrrolidino, R₃ = R₅ = H, R₄ = SO₂Me) was prepd. Data for biol. activity of I were given.

L64 ANSWER 21 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:385518 HCAPLUS

DN 129:23446

TI **Antipruritic agent**

IN Nagase, Hiroshi; Utsumi, Jun; Endoh, Takashi; Tanaka, Toshiaki; Kamei, Junzo; Kawamura, Kuniaki

PA Toray Industries, Inc., Japan; Nagase, Hiroshi; Utsumi, Jun; Endoh, Takashi; Tanaka, Toshiaki; Kamei, Junzo; Kawamura, Kuniaki

SO PCT Int. Appl., 92 pp.

CODEN: PIXXD2

DT Patent

LA Japanese

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9823290	A1	19980604	WO 1997-JP4267	19971121 <--
	W: AU, CA, CN, JP, KR, NO, NZ, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	CA 2244256	AA	19980604	CA 1997-2244256	19971121 <--
	AU 9749683	A1	19980622	AU 1997-49683	19971121 <--
	AU 738743	B2	20010927		
	EP 897726	A1	19990224	EP 1997-912539	19971121 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
	CN 1214634	A	19990421	CN 1997-193343	19971121 <--
	NO 9803431	A	19980924	NO 1998-3431	19980724 <--
	US 6174891	B1	20010116	US 1998-117052	19980824 <--
	US 6316461	B1	20011113	US 2000-615540	20000713 <--
PRAI	JP 1996-313476	A	19961125 <--		
	WO 1997-JP4267	W	19971121		
	US 1998-117052	A3	19980824		

OS MARPAT 129:23446

AB An antipruritic agent comprising an opioid .
kappa. receptor agonist which is useful for
the treatment of **pruritus** in various diseases accompanied by
pruritus, morphinan quaternary ammonium salt derivs. and morphinan
N-oxide derivs. Thus, 17-cyclopropylmethyl-3,14.beta.-dihydroxy-
4,5.alpha.-epoxy-6.beta.-[N-methyl-trans-3-(3-furyl)acrylamido]morphinan
2.0699 g was reacted with 1.3 mL Me iodide to give 17-cyclopropylmethyl-
3,14.beta.-dihydroxy-4,5.alpha.-epoxy-17-methyl-6.beta.-[N-methyl-trans-3-
(3-furyl)acrylamido]morphinan iodide 102 mg, which showed Ke value 16.67
nM in the presence of a .mu. antagonism naloxone (100 nM) for an ileum
sample of guinea pig, and Ke value 14.18 nM in the presence of naloxone
(30 nM) for a spermatic duct of a mouse.

L64 ANSWER 22 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:366889 HCAPLUS

DN 129:58790

TI anti-pruritic .kappa.-agonist pharmaceutical
formulations and method of treating pruritus therewith

IN Farrar, John J.; Chang, An-chih; Kumar, Virendra;
Zhang, Wei Yuan; Cowan, Alan

PA Adolor Corp., USA

S0 U.S., 21 pp.

CODEN: USXXAM

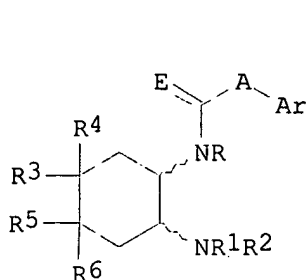
DT Patent

LA English

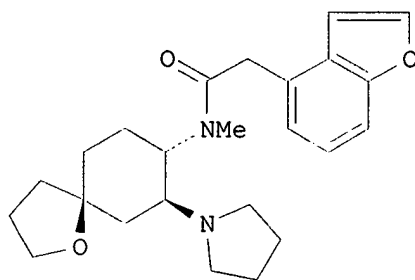
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5760023	A	19980602	US 1997-892599	19970714
	US 5869521	A	19990209	US 1998-64695	19980422
	WO 9903459	A1	19990128	WO 1998-US12789	19980619
	W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, GW, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LS, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9884719	A1	19990210	AU 1998-84719	19980619
	AU 740566	B2	20011108		
	EP 996434	A1	20000503	EP 1998-935477	19980619
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	BR 9810706	A	20000808	BR 1998-10706	19980619
	ZA 9806206	A	19990209	ZA 1998-6206	19980713
	US 6004964	A	19991221	US 1998-184393	19981102
	US 6048860	A	20000411	US 1999-411111	19991004

NO 9906353 A 20000313 NO 1999-6353 19991220
 US 6156769 A 20001205 US 2000-488420 20000120
 PRAI US 1997-892599 A3 19970714
 US 1998-64695 A 19980422
 WO 1998-US12789 W 19980619
 US 1998-184393 A3 19981102
 US 1999-411111 A3 19991004
 OS MARPAT 129:58790
 GI



I



II

AB Anti-pruritic pharmaceutical formulations contg. **.kappa**
 .-agonist cyclohexanediamine derivs. I (A = bond, (CH₂)_q, CHMe,
 X(CH₂)_n; q = 1-4; n = 1-4; X = O, S; Ar = (un)substituted arom.
 hetero-arom., bicyclic-arom., tricyclic-arom., diphenylmethyl; R, R1, R2
 independently are H, C1-3 alkyl, allyl; R1R2 may form a ring consisting of
 azetidiny, pyrrolidiny, 3-hydroxypyrrolidiny, 3-fluoropyrrolidiny,
 morpholinyl, piperidiny, 3,4-dehydropiperidiny; R3, R4, R5, R6 = H, OH,
 alkoxy, alkoxy carbonyl; R5R6 = ECH₂CH₂E; R5R6 may form a satd. 5-membered
 ring contg O, nitrogen, S, S(O), S(O)₂; E = NOH, NOAc, O, S) were prepd.
 for prevention or treatment of **pruritus** in a mammal with the
 anti-pruritic formulations. Thus, the **antipruritic**
 activity was detd. by redn. of **scratching** of mice injected with
 II had 75% inhibition at 10 mg/kg s.c. Several pharmaceutical compns. of
 the compds. were mixed with a suitable pharmaceutical carrier or vehicle
 for systemic, topical or local administration.

L64 ANSWER 23 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:331568 HCAPLUS

DN 129:614

TI Methods for treatment and prevention of drug-induced **pruritus**
 with serotonin type 3 receptor antagonists

IN Larijani, Ghassem E.

PA USA

SO U.S., 3 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5756514	A	19980526	US 1996-775455	19961230 <--

AB Methods are provided for treating and preventing **pruritus**
 induced by drugs (e.g. opioids or antibiotics) in patients by
 administration of a serotonin type 3 antagonist, e.g. ondansetron-HCl.

L64 ANSWER 24 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:141181 HCAPLUS

TI Arylacetamides as peripheral **kappa** agonists.

AU Marella, M.; Cortes-Burgos, L.; Daubert, J.; DeHaven, R.; DeHaven-Hudkins,
 D.; Gottshall, S.; Maycock, A.

CS Adolor Corporation, Malvern, PA, 19355, USA

SO Book of Abstracts, 215th ACS National Meeting, Dallas, March 29-April 2

(1998), MEDI-151 Publisher: American Chemical Society, Washington, D. C.
CODEN: 65QTAA

DT Conference; Meeting Abstract

LA English

AB The therapeutic potential of **opioids** acting in the central nervous system(CNS) to alleviate pain is well established. **Opiate receptors** (.mu., .kappa., and .delta.) are present in the central and peripheral nervous system of many species, including human. Antinociception in animals and humans can be produced by activation of these **receptors** within the CNS and there is mounting evidence that **opioid receptor-mediated** antinociception occurs in the periphery. Selective **.kappa. agonists** should be effective analgesics devoid of many side effects that are assocd. with .mu. **agonists**, such as respiratory depression, constipation, and phys. dependence. However, preclin. and clin. studies with centrally active **.kappa. agonists** have revealed undesired properties such as sedation, diuresis and dysphoria. Strategies at Adolor are to explore the peripherally acting **.kappa. receptor agonists** that have limited or no CNS access in an effort to reduce or eliminate these side effects. To achieve this goal, analogs of known centrally active **.kappa. agonists** such as ICI 199441 (1) have been structurally modified to give the compds. of the general structure (2) without any deleterious effects on the binding or selectivity to the **.kappa. receptor**. The syntheses, structure-activity relationships, and in vitro and in vivo data of these compds. will be presented.

L64 ANSWER 25 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1997:752779 HCAPLUS

DN 128:34783

TI **Kappa agonist** compounds (acylpiperazines and analogs) and pharmaceutical formulations thereof

IN Kruse, Lawrence I.; Chang, An-chih; Dehaven-Hudkins, Diane L.; Farrar, John J.; Gaul, Forrest; Kumar, Virendra; Marella, Michael Anthony; Maycock, Alan L.; Zhang, Wei Yuan

PA **Adolor Corp., USA**

SO U.S., 65 pp. Cont.-in-part of U.S. Ser. No. 612,680.

CODEN: USXXAM

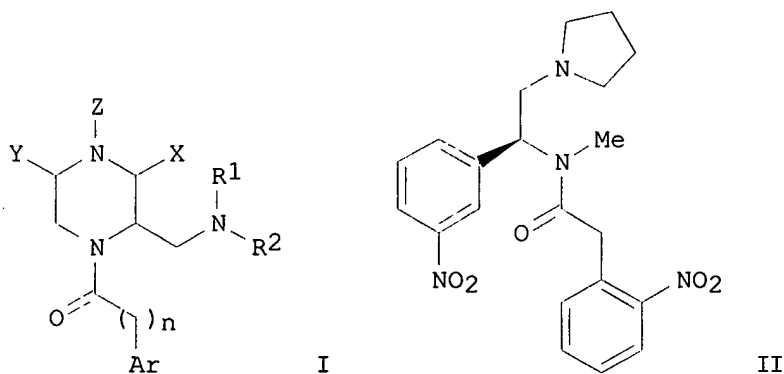
DT Patent

LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5688955	A	19971118	US 1997-796078	19970205
	US 5646151	A	19970708	US 1996-612680	19960308
	CA 2240728	AA	19970912	CA 1997-2240728	19970301
	AU 9721954	A1	19970922	AU 1997-21954	19970301
	AU 717126	B2	20000316		
	BR 9707958	A	20000104	BR 1997-7958	19970301
	US 5763445	A	19980609	US 1997-891833	19970714
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 5981513	A	19991109	US 1998-45522	19980321
	NO 9804107	A	19981109	NO 1998-4107	19980907
	US 6303611	B1	20011016	US 1998-150369	19980909
	US 6057323	A	20000502	US 1998-183011	19981030
	US 6028063	A	20000222	US 1999-307517	19990507
	US 6054445	A	20000425	US 1999-307387	19990507
	US 6239154	B1	20010529	US 1999-372191	19990811
	US 6180623	B1	20010130	US 1999-436057	19991108
	NO 2001004219	A	19981109	NO 2001-4219	20010831
	NO 2001004220	A	19981109	NO 2001-4220	20010831
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A	19970205		
	WO 1997-US3353	W	19970301		
	US 1997-891833	A3	19970714		

US 1997-899086 A3 19970723
 US 1998-34661 A2 19980303
 US 1998-45522 A3 19980321
 US 1998-150369 A2 19980909
 US 1998-183011 A3 19981030
 US 1999-307517 A3 19990507
 OS MARPAT 128:34783
 GI



AB Compds. having **kappa opioid agonist** activity, compns. contg. them, and methods of using them as analgesics are provided. The compds. have 4 general structures, e.g., I [n = 1-3; R1 = R2 = Me; or NR1R2 forms various cyclic systems; Ar = (un)substituted Ph, benzothienyl, benzofuranyl, naphthyl, CHPh2, or 9-fluorenyl; Z = wide variety of sidechains; X, Y = various derivs. of CH2OH and CH2NH2]. A large no. of compds., as HCl salts and/or free bases, were prepd., tested, and/or claimed. For instance, title compd. II.HCl, i.e. ADL-01-0115-4, was prepd. in 51% yield by amidation of 2-nitrophenylacetic acid with the corresponding secondary amine using DCC and pyridine in CH2Cl2. In tests for displacement of [3H]-diprenorphin or [3H]-U-69593 from **kappa receptors** in vitro, II.HCl had Ki values of 35 and 3.2 nM, resp.

L64 ANSWER 26 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1997:616927. HCAPLUS
 DN 127:283391

TI Pharmaceutical compositions containing film-forming
antihyperalgesic opiates for treatment of hyperalgesic conditions
 IN Farrar, John J.; Maycock, Alan L.; Kumar, Virendra; Balogh, Imre
 PA Adolor Corp., USA
 SO U.S., 11 pp.
 CODEN: USXXAM

DT Patent
 LA English

FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5667773	A	19970916	US 1996-614027	19960312
	CA 2223514	AA	19970918	CA 1997-2223514	19970226
	WO 9733634	A1	19970918	WO 1997-US3315	19970226
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN			
	RW:	AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE			
	AU 9719847	A1	19971001	AU 1997-19847	19970226
	AU 715912	B2	20000210		
	EP 888141	A1	19990107	EP 1997-907990	19970226

R: DE, FR, GB
 US 5888494 A 19990330 US 1997-891924 19970714
 PRAI US 1996-614027 A 19960312
 WO 1997-US3315 W 19970226
 AB Topical anti-hyperalgesic film-forming compns. and methods of using compns. for the treatment of peripheral hyperalgesia comprise (a) **antihyperalgesic** opiates; (b) a film-forming polymeric material; and (c) an aq. pharmaceutically acceptable carrier. A pharmaceutical compn. contained loperamide.HCl 25.0, sodium carrageenan 25.0, calcium lactate 32.0, and water q.s. 100.0%.

L64 ANSWER 27 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1997:456146 HCAPLUS

DN 127:152946

TI Pharmaceutical formulations containing **.kappa.-opioid agonists**

IN Kruse, Lawrence I.; Kumar, Virendra; Chang, An-chih; Dehaven-Hudkins, Diane L.; Farrar, John J.; Maycock, Alan L.

PA **Adolor Corp., USA**

SO U.S., 26 pp.

CODEN: USXXAM

DT Patent

LA English

FAN.CNT 7

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5646151	A	19970708	US 1996-612680	19960308
	US 5688955	A	19971118	US 1997-796078	19970205
	CA 2240728	AA	19970912	CA 1997-2240728	19970301
	WO 9732857	A1	19970912	WO 1997-US3353	19970301
	W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	AU 9721954	A1	19970922	AU 1997-21954	19970301
	AU 717126	B2	20000316		
	EP 885199	A1	19981223	EP 1997-914850	19970301
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
	BR 9707958	A	20000104	BR 1997-7958	19970301
	US 5763445	A	19980609	US 1997-891833	19970714
	US 5744458	A	19980428	US 1997-899086	19970723
	US 5945443	A	19990831	US 1998-34661	19980303
	US 5981513	A	19991109	US 1998-45522	19980321
	NO 9804107	A	19981109	NO 1998-4107	19980907
	US 6303611	B1	20011016	US 1998-150369	19980909
	US 6057323	A	20000502	US 1998-183011	19981030
	US 6028063	A	20000222	US 1999-307517	19990507
	US 6054445	A	20000425	US 1999-307387	19990507
	US 6239154	B1	20010529	US 1999-372191	19990811
	US 6180623	B1	20010130	US 1999-436057	19991108
	NO 2001004219	A	19981109	NO 2001-4219	20010831
	NO 2001004220	A	19981109	NO 2001-4220	20010831
PRAI	US 1996-612680	A2	19960308		
	US 1997-796078	A	19970205		
	WO 1997-US3353	W	19970301		
	US 1997-891833	A3	19970714		
	US 1997-899086	A3	19970723		
	US 1998-34661	A2	19980303		
	US 1998-45522	A3	19980321		
	US 1998-150369	A2	19980909		
	US 1998-183011	A3	19981030		
	US 1999-307517	A3	19990507		

OS MARPAT 127:152946

AB Pharmaceutical formulations contg. **.kappa.-opioid agonists** (Markush structure given) are claimed. A capsule

contained active compd. 2.5, corn starch 23.0, lactose 145.0, talc 15.0, and magnesium stearate 3.0 g.

L64 ANSWER 28 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1997:332024 HCAPLUS
DN 126:308827
TI Peripherally active anti-hyperalgesic opiates
IN Yaksh, Tony L.; Farrar, John J.; Maycock, Alan L.; Lewis, Michael E.; Dow, Gordon J.
PA Regents of the University of California, USA; Adolor Corporation
; Yaksh, Tony L.; Farrar, John J.; Maycock, Alan L.; Lewis, Michael E.; Dow, Gordon J.
SO PCT Int. Appl., 317 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9709973	A2	19970320	WO 1996-US14727	19960912
	WO 9709973	A3	19970605		
	W:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG			
	US 5849761	A	19981215	US 1995-528510	19950912
	CA 2229814	AA	19970320	CA 1996-2229814	19960912
	AU 9670710	A1	19970401	AU 1996-70710	19960912
	AU 727982	B2	20010104		
	EP 852494	A2	19980715	EP 1996-931567	19960912
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI			
	BR 9610345	A	19990601	BR 1996-10345	19960912
	JP 11512438	T2	19991026	JP 1996-512136	19960912
	NO 9800700	A	19980512	NO 1998-700	19980219
	US 6166039	A	20001226	US 1998-199873	19981124
PRAI	US 1995-528510	A	19950912		
	WO 1996-US14727	W	19960912		
OS	MARPAT 126:308827				
AB	Compns. and methods using the compns. for treatment of peripheral hyperalgesia are provided. The compns. contain an anti-hyperalgesia effective amt. of one or more compds. that directly or indirectly interact with peripheral opiate receptors , but that do not, upon topical or local administration, elicit substantial central nervous system effects. The anti-diarrheal compd. loperamide-HCl is preferred for use in the compns. and methods.				

L64 ANSWER 29 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:719992 HCAPLUS
DN 126:211
TI Ondansetron: A review of its pharmacology and preliminary clinical findings in novel applications
AU Wilde, Michelle I.; Markham, Anthony
CS Adis International Limited, Auckland, N. Z.
SO Drugs (1996), 52(5), 773-794
CODEN: DRUGAY; ISSN: 0012-6667
PB Adis
DT Journal; General Review
LA English
AB A review with 185 refs. The use of ondansetron, a selective serotonin 5-HT3 **receptor** antagonist, is well established in patients with nausea and vomiting assocd. with cancer chemotherapy, radiotherapy or anesthesia and surgery. The wide distribution of 5-HT3 **receptors**

in the body and the role of these **receptors** in disease have provided the rationale for investigation of ondansetron in novel applications. Preliminary data have shown ondansetron to have clin. benefit in patients with nausea and vomiting assocd. with drug overdosage or poisoning, antiinfective or antidepressant therapies, uremia or neurol. trauma, and in patients with **pruritus**. Patients with gastrointestinal motility disorders (e.g. carcinoid syndrome, irritable bowel syndrome, diarrhea assocd. with cryptosporidiosis or diabetes, and chronic refractory diarrhea) have also shown some improvement when treated with ondansetron, as have patients with certain pain or CNS-related disorders [e.g. alc. (ethanol) dependence, **opiate** withdrawal, vertigo, cerebellar tremor and Parkinson's disease treatment-related psychosis]. In contrast to conventional antiemetics, ondansetron is generally well tolerated with a lower incidence of sedation and only isolated case reports of extrapyramidal reactions. Furthermore, unlike dopamine **receptor**-blocking neuroleptics, ondansetron does not appear to worsen the symptoms of Parkinson's disease. Thus, in addn. to its established indications, preliminary results suggest that ondansetron may be beneficial in a no. of novel applications. This drug may represent a treatment alternative in patients with refractory disease, or an effective treatment of conditions for which current therapies are either poorly tolerated or not available. Further investigation of ondansetron in a range of potential new applications appears to be warranted.

L64 ANSWER 30 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:654315 HCAPLUS
DN 125:298242
TI Pathophysiology of **itching**
AU Greaves, M. W.; Wall, P. D.
CS St John's Institute Dermatology, St Thomas' Hospital, London, SE1 7EH, UK
SO Lancet (1996), 348(9032), 938-940
CODEN: LANCAO; ISSN: 0140-6736
DT Journal; General Review
LA English
AB A review with 30 refs. **Itching** is the predominant symptom of skin disease but it is ill-understood and a challenge for future research. Even the major nerve pathways for **itch**, and its relation to pain are debatable. In inflamed skin, histamine plays a major role and its mode of release from mast cells in, for example, chronic urticaria is now better appreciated. Tachykinins including substance P and cytokines including interleukin-2 are evidently important peripherally. **Opioid .mu.-receptor**-dependent processes activate inhibitory circuits in the central nervous system and regulate the extent of intensity and quality of perceived **itch**. It is proposed that stimulation of large areas of skin such as by **scratching**, generates inhibitory activity which suppresses **itch** excitation. Therapeutic intervention based upon understanding these regulatory processes is a real prospect.

L64 ANSWER 31 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1996:236396 HCAPLUS
DN 124:307370
TI Naloxone versus nalbuphine infusion for prophylaxis of epidural morphine-induced **pruritus**
AU Kendrick, Will D.; Woods, Andrew M.; Daly, Martha Y.; Birch, Robert F. H.; DiFazio, Cosmo
CS Health Sciences Center, University Virginia, Charlottesville, VA, 22908, USA
SO Anesth. Analg. (Baltimore) (1996), 82(3), 641-7
CODEN: AACRAT; ISSN: 0003-2999
DT Journal
LA English
AB This randomized, double-blind study compared the efficacy of two .mu.-receptor antagonists, naloxone and nalbuphine, in the prophylactic management of **pruritus** in postcesarean section patients receiving epidural morphine. Dosages of study drugs were individualized

by the use of a patient self-administration (PSA) device. All 51 patients were healthy women who received a uniform epidural anesthetic and epidural morphine (5 mg). Coded solns. were infused for 24 h, with 5-min PSA lockout times: Group A (n = 17), nalbuphine 2.5 mg/h, PSA nalbuphine 1 mg; Group B (n = 16), naloxone 50 .mu.g/h, PSA saline; Group C (n = 18), naloxone 50 .mu.g/h, PSA naloxone 40 .mu.g. Patients were assessed for **pruritus** and pain every 8 h for 24 h. Both naloxone and nalbuphine provided good relief for **pruritus**; median pain and **pruritus** scores were in the none-to-mild range (0-3) for all groups at all assessment intervals. The **pruritus** scores of the PSA saline group were higher during the 16- to 24-h period (P < 0.05) than the scores of either group receiving .mu.-receptor antagonist by PSA. There was evidence of shortening of the duration of analgesia in patients receiving naloxone who required treatment for **pruritus** after 16 h. Patients who self-administered large doses of nalbuphine over the first 8 h also reported pain scores consistent with reversal of analgesia. The potency ratio for naloxone:nalbuphine for antagonism of the **pruritic** effects of epidural morphine was approx. 40:1. Intervention to treat either unrelieved **pruritus** or pain, resp., was necessary in the following nos. of patients: Group A, 0/1; Group B, 1/1; Group C, 2/2. Prophylactic infusions offer the potential for labor cost savings by minimizing the need for episodic therapeutic interventions to treat **pruritus**.

L64 ANSWER 32 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1995:865334 HCAPLUS

DN 123:306413

TI Microinjection of morphine into the rat medullary dorsal horn produces a dose-dependent increase in facial **scratching**

AU Thomas, David A.; Hammond, Donna L.

CS Department of Anesthesia and Critical Care, University of Chicago MC 4028, 5841 South Maryland Ave., Chicago, IL, 60637, USA

SO Brain Res. (1995), 695(2), 267-70

CODEN: BRREAP; ISSN: 0006-8993

DT Journal

LA English

AB It has been proposed that **opioids** act at the level of the medulla to produce facial **pruritus**. Supporting this hypothesis, microinjection of .mu.-**opioid receptor agonists** into the medullary dorsal horn (MDH; trigeminal subnucleus caudalis) of monkeys produces facial **scratching** behavior. The present study sought to establish a rodent model of **opioid-induced facial pruritus**. To this end, morphine (0.1, 0.3 or 1.0 .mu.g/0.2 .mu.l) or saline (0.2 .mu.l) was unilaterally microinjected into the MDH of male Sprague-Dawley rats. Behavior for the 20 min preceding and the 80 min after this microinjection was videotaped. Morphine produced dose-dependent increases in facial **scratching** behavior ipsilateral to the microinjections with the peak effect at 30-40 min after microinjection. Facial **scratching** continued for the entire 80 min post-microinjection test period. Morphine also produced a lesser degree of facial **scratching** contralateral to the microinjections. Increases in facial **scratching** ipsilateral to the microinjection of 0.3 .mu.g morphine into the MDH were attenuated by 0.4 mg/kg s.c. naloxone. These findings support the hypothesis that the MDH is a crit. site of action of **opioid agonists** in producing facial **pruritus**.

L64 ANSWER 33 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1995:749737 HCAPLUS

DN 123:159898

TI Remifentanyl pharmacokinetics and pharmacodynamics. A preliminary appraisal

AU Egan, Talmage D.

CS Dep. Anesthesiology, Univ. Utah Sch. Med., Salt Lake City, UT, USA

SO Clin. Pharmacokinet. (1995), 29(2), 80-94

CODEN: CPKNDH; ISSN: 0312-5963

DT Journal; General Review

LA English

AB A review with 41 refs. Remifentanyl is a novel, short-acting **.mu.-receptor opioid agonist** currently in the late stages of development. A member of the 4-anilidopiperidine class, it is unique among the currently marketed agents because of its ester structure. Remifentanyl undergoes widespread extrahepatic metab. by blood and tissue nonspecific esterases, resulting in an extremely rapid clearance of approx. 3 L/min (180 L/h). Like the other members of this class of drugs, remifentanyl is lipophilic and is widely distributed in body tissues with a steady-state vol. of distribution of approx. 30L. Because of its unique metabolic pathway (among this group of drugs) and rapid clearance, remifentanyl represents a new pharmacokinetic class of **opioid**. Unlike the other fentanyl congeners, termination of the therapeutic effect of remifentanyl mostly depends on metabolic clearance rather than on redistribution. The context-sensitive half-time [defined as the time necessary to achieve a 50% decrease in blood (or plasma) concn. after termination of a variable length, continuous infusion targeted to maintain a steady-state concn., where the 'context' is the duration of the infusion] is strikingly short for remifentanyl, and this is perhaps the most compelling evidence of the pharmacokinetic singularity of the drug. Detd. by computer simulation, the context-sensitive half-time of remifentanyl is approx. 3 min, and is independent of infusion duration. Pharmacodynamically, remifentanyl is similar to the other fentanyl congeners. The drug produces physiol. changes consistent with potent **.mu.-receptor agonist** activity, including analgesia and sedation. Its adverse effect profile (like that of the other drugs of this class) includes ventilatory depression, nausea, vomiting, muscular rigidity, bradycardia and **pruritus**. Because it does not release histamine upon injection, remifentanyl has fewer hemodynamic adverse effects than morphine. The therapeutic potency of remifentanyl is somewhat less than that of fentanyl, with an effective concn. (producing 50% of maximal effect, as measured by electroencephalog.) of approx. 15 to 20 **.mu.g/L**. Speed of onset of effect is very rapid and is similar to that of alfentanil, which is reflected in a $t_{1/2keo}$ (a parameter used to characterize the delay between peak blood drug concn. and peak pharmacodynamic effect utilising a theor. effect compartment) of approx. 1 to 2 min. Remifentanyl is likely to be a welcome addn. to the anesthesia drug formulary. Anesthetists have long recognized the need for a short acting **opioid** with a predictable pharmacokinetic profile. Because the length of surgical procedures is often unpredictable, and because the level of surgical stimulation against which the depth of anesthesia must be balanced is highly variable and dynamic, the advantages of predictably short-acting agents are obvious.

L64 ANSWER 34 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1995:728598 HCAPLUS

DN 123:102497

TI Effects of naloxone infusions in patients with the **pruritus** of cholestasis: a double-blind, randomized, controlled trial

AU Bergasa, Nora Valeria; Alling, David W.; Talbot, Thomas L.; Swain, Mark G.; Yurdaydin, Cihan; Turner, Maria L.; Schmitt, Joseph M.; Walker, Elijah C.; Jones, E. Anthony

CS Nat. Inst. Health, Bethesda, MD, USA

SO Ann. Intern. Med. (1995), 123(3), 161-7

CODEN: AIMEAS; ISSN: 0003-4819

DT Journal

LA English

AB This is to det. whether endogenous **opioids** contribute to the **pruritus** of cholestasis by studying the effect of the **opiate** antagonist naloxone on the perception of **pruritus** and on **scratching** activity in patients with this form of **pruritus**. The design is a double-blind, placebo-controlled, crossover trial with four periods. 29 **Pruritic** patients were used with liver diseases of various causes. Each patient received as many as two naloxone and two placebo soln. infusions consecutively in random

order. During the infusions, visual analog scores of **pruritus** were recorded every 4 h while patients were awake; **scratching** activity independent of limb movements was recorded continuously. One patient had a mild reaction consistent with a naloxone-pptd. syndrome similar to **opiate** withdrawal. A significant 24-h rhythm of **scratching** activity was seen in 7 of 11 patients for whom complete 96-h data were collected. The mean of a visual analog score of the perception of **pruritus** (max., 10.0) recorded during naloxone infusions was 0.582 lower than that recorded during placebo infusions (95% CI, 0.176 to 0.988; $P < 0.01$). The ratio of the geometric mean hourly **scratching** activity during naloxone infusions to that during placebo infusions was 0.727 (CI, 0.612 to 0.842; $P < 0.001$) and was greater than 1.0 in only five patients. Naloxone administration is assocd. with amelioration of the perception of **pruritus** and redn. of **scratching** activity in cholestatic patients. Because of the **opioid receptor** specificity of the action of naloxone, these findings support the hypothesis that a mechanism underlying the **pruritus** of cholestasis is modulated by endogenous **opioids** and suggest that **opiate** antagonists may have a role in the management of this complication of cholestasis.

L64 ANSWER 35 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1994:691791 HCAPLUS
 DN 121:291791
 TI Alpha-2 agonists and analgesia
 AU Eisenach, James C
 CS Medical Center, Wake Forest University, Winston-Salem, NC, 27157-1009, USA
 SO Expert Opin. Invest. Drugs (1994), 3(10), 1005-10
 CODEN: EOIDER; ISSN: 0967-8298
 DT Journal; General Review
 LA English
 AB A review, with 29 refs. In addn. to their anti-hypertensive effects, alpha-2 **agonists** also cause analgesia. Since analgesia from these drugs is due primarily to actions in the spinal cord, it is not surprising that analgesia is poor after systemic administration, but profound after injection near the cord (spinal or epidural administration). Advantages of alpha-2 **agonists** over **opioids** in the treatment of severe pain include lack of **opioid** type side effects (addiction, nausea, respiratory depression, **pruritus**), lack of abuse potential and efficacy in special situations where **opioids** fail (**opioid** tolerance, neuropathic pain, reflex sympathetic dystrophy). Clonidine, the lead compd. in this category, has been administered epidurally or spinally to over 1,000 patients in published reports, and detailed cerebrospinal fluid pharmacokinetics and pharmacodynamics have been described. Epidural clonidine has been designated as an orphan product in the US for the treatment of intractable cancer pain, and a multi-center, placebo-controlled, Phase III trial has demonstrated its safety and efficacy for this indication. As might be expected, epidural clonidine is effective in the setting of **opioid** tolerance, neuropathic pain and reflex sympathetic dystrophy, but is also effective alone and in combination with other analgesics in the treatment of postoperative and obstetric labor pain. Dexmedetomidine is the only other alpha-2 **agonist** under clin. development in injectable form. Although dexmedetomidine is a more potent and selective alpha-2 **agonist** than clonidine, its high lipid soly. leads to rapid systemic absorption after intraspinal use, which will probably lead to sedation and decreased blood pressure. Development of hydrophilic alpha-2 **agonists**, such as ST-91 and oxymetazoline, could offer unique advantages for this indication.

L64 ANSWER 36 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1994:261151 HCAPLUS
 DN 120:261151
 TI Multiple effects of morphine on facial **scratching** in monkeys
 AU Thomas, David A.; Williams, Gene M.; Iwata, Koichi; Kenshalo, Daniel R.

Jr.; Dubner, Ronald

CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA

SO Anesth. Analg. (N. Y.) (1993), 77(5), 933-5
CODEN: AACRAT; ISSN: 0003-2999

DT Journal

LA English

AB The medullary dorsal horn (MDH), the medullary homolog of the spinal dorsal horn, is a site where **opioid-receptor agonists** can act at **opioid receptors** to produce pronounced facial **scratching**, the behavioral correlate of **pruritus**. In the present study, after a 10-min baseline period, morphine (5.0 .mu.g) was microinjected into the MDH of monkeys. Behavior was videotaped and facial **scratches** were counted by two independent raters. Morphine greatly increased facial **scratching** behavior, which is consistent with previous findings where .mu.-**opioid receptor agonists** microinjected into the MDH have been to induce dose-dependent, naloxone-reversible facial **scratching** in monkeys. In the current research, i.m. administration of the **opioid-receptor** antagonist, naloxone (0.5 mg/kg), reversed this MDH morphine-induced **scratching**. Addnl., i.m. morphine (1.0 mg/kg) produced a substantial redn. in facial **scratching** behavior. **Scratching** behavior continued at a high rate after injection of saline (0.1 mL/kg, i.m.). These findings support the hypothesis that morphine has both pruragenic and antipruragenic activity, depending on the site of action.

L64 ANSWER 37 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1994:154462 HCAPLUS

DN 120:154462

TI Noradrenergic and opioid systems interact to alter the detection of noxious thermal stimuli and facial **scratching** in monkeys

AU Thomas, David A.; Anton, Fernand; Kenshalo, Daniel R. Jr.; Williams, Gene M.; Dubner, Ronald

CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA

SO Pain (1993), 55(1), 63-70
CODEN: PAINDB; ISSN: 0304-3959

DT Journal

LA English

AB The authors examd. the ability of the .alpha.2-adrenoceptor **agonist**, ST-91, microinjected into the medullary dorsal horn (MDH), to diminish the sensory-discriminative features of noxious heat stimuli in awake behaving monkeys. Two monkeys performed a noxious thermal detection task and the time to detection of small increases in heat served as a measure of the perceived intensity of pain. ST-91 microinjected into the MDH (1.0, 3.0, 10.0 and 30.0 .mu.g/0.4 .mu.L) produced dose-dependent increases in detection time to graded temp. increases (0.4-1.0.degree.) from a noxious 46.degree. base line. These dose-dependent effects were attenuated by the systemic administration of the .alpha.2-adrenoceptor antagonist, idazoxan (2.0 mg/kg, i.m.), but not by the .alpha.1-adrenoceptor antagonist, prazosin (0.5 mg/kg, i.m.) or the **opioid-receptor** antagonist, naloxone (0.5 mg/kg, i.m.). The effect of ST-91 on detection latency of thermal stimuli was not the result of alterations in attentional, motivational or motoric aspects of the monkeys' behavior, because detection of visual stimuli and non-noxious temp. coolings (36.0-34.5.degree.) in a similar paradigm were not consistently altered. Microinjection of morphine (3.0 mg) into the MDH also increased detection latency of the noxious heat stimuli. Systemic administration of the **opioid-receptor** antagonist, naloxone (0.5 mg/kg), and the .alpha.2-adrenoceptor antagonist, idazoxan (2.0 mg/kg, i.m.) attenuated these effects of morphine. In a sep. expt., morphine (5.0 .mu.g) microinjected into the MDH induced facial **scratching** behavior. Idazoxan (2.0 mg/kg) was effective at attenuating this **scratching** behavior. The authors have thus

shown participation of MDH .alpha.2-adrenoceptors in the process underlying the perception of the intensity of noxious thermal stimulation in monkeys. Further, **opioid** and noradrenergic systems interacted in the noxious heat detection paradigm and a paradigm where facial **scratching** behavior was studied.

L64 ANSWER 38 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1993:641300 HCAPLUS

DN 119:241300

TI The medullary dorsal horn. A site of action of morphine in producing facial **scratching** in monkeys

AU Thomas, David A.; Williams, Gene M.; Iwata, Koichi; Kenshalo, Daniel R., Jr.; Dubner, Ronald

CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA

SO Anesthesiology (1993), 79(3), 548-54

CODEN: ANESAV; ISSN: 0003-3022

DT Journal

LA English

AB **Pruritus** is a common side effect of epidural and intrathecal morphine administration in humans. This naloxone-reversible **pruritus** is typically present on the trunk, but is often severe around the eyes and nose, of the patients. The brain stem was proposed as the site where **opioids** act to produce this effect. The authors studied the effect of morphine administered into the medullary dorsal horn (MDH), the brain stem homolog of the spinal dorsal horn, on facial-**scratching** behavior in monkeys. Morphine was unilaterally microinjected into the MDH of rhesus monkeys. Systemic injections of the **opioid-receptor** antagonist naloxone (0.5 mg/kg i.m.) were also made in combination with morphine microinjection. Systemic injections of the antihistamine chlorcyclizine (1.0 and 2.5 mg/kg i.m.) were also made to det. if facial **scratching** was mediated through histamine release. The monkeys were videotaped for 10-15 min before and 1-2 h after **opioid** microinjection, and the no. and location of **scratches** were counted. A dose-response curve was established for the .mu./delta.-**opioid-receptor** agonist morphine (0.5, 1.0, 2.5, and 5.0 .mu.g). Specificity of the site of action within the MDH was examd. by systematically changing the microinjection site, and examg. the area of the face that the monkeys **scratched**. Morphine produced large dose-dependent increases in facial **scratching** ipsilateral to the microinjection. Increases in facial **scratching** were also obsd. contralateral to the microinjections. These effects were reversed by naloxone. The facial area **scratched** after microinjection of morphine was directly related to the injection site, with 1-mm changes in the location of the microinjection resulting in pronounced changes in the area of the face that the monkeys **scratched**. Systemic injection of chlorcyclizine produced only a small, transient attenuation of morphine's effect. Data from this study demonstrate that the MDH is a site where morphine acts to produce facial **scratching** in monkeys by acting at **opioid receptors**. Also probably the MDH is a site where centrally administered **opioids** act in producing facial **pruritus** in humans. The effects of morphine on facial-**scratching** behavior were only modestly attenuated with chlorcyclizine, indicating a minor involvement of a histamine-dependent mechanism of action.

L64 ANSWER 39 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1993:400816 HCAPLUS

DN 119:816

TI Pharmacologic characteristics of a medullary **hyperalgesic center**

AU Parvini, Shirin; Hamann, Scott R.; Martin, William R.

CS Dep. Pharmacol. Anesthesiol., Univ. Kentucky, Lexington, KY, USA

SO J. Pharmacol. Exp. Ther. (1993), 265(1), 286-93

CODEN: JPETAB; ISSN: 0022-3565

DT Journal
 LA English
 AB The effects of ethylketazocine, U-50,488, morphine and (-)-nicotine administered both i.p. and into the mid-fourth ventricle of intact rats were investigated using a conventional high intensity tail-flick reflex and one evoked with a lower intensity thermal stimulus. The sensitivity of the low intensity thermally evoked tail avoidance reflex was several times that of a high intensity tail-flick reflex in detecting the analgesic activity of morphine and yielded valid assays and relative potencies between morphine, EKC (18.76) and U-50,488 (0.23) when the drugs were administered i.p. When the **opioid** drugs were administered into the fourth ventricle they produced a dose-related shortening of the latency of the low intensity thermally evoked tail avoidance reflex. (-)-Nicotine, when administered into the mid-fourth ventricle, produced analgesia in low doses and hyperalgesia in high doses. Naltrexone and mecamylamine, when administered into the fourth ventricle, produced a dose-related analgesia. Doses of naltrexone and mecamylamine which antagonize maximally hyperalgesic doses of (-)-nicotine and ethylketazocine did not produce analgesia; however, larger doses produced analgesia. These observations suggest that analgesic doses do not involve prototypic **.kappa.-opioidergic** or nicotinic mechanisms. These data confirm the existence of a medullary hyperalgesic center which may have both **.mu.-** and **.kappa.-opioidergic** as well as nicotinic mechanisms. Furthermore, these data indicate that this medullary hyperalgesic mechanism may have spontaneous or evoked tone and provide an explanation for the analgesic action of naltrexone and mecamylamine.

L64 ANSWER 40 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1992:543892 HCAPLUS

DN 117:143892

TI Effects of central administration of opioids on facial **scratching** in monkeys

AU Thomas, D. A.; Williams, G. M.; Iwata, K.; Kenshalo, D. R., Jr.; Dubner, R.

CS Neurobiol. Anesthesiol. Branch, Natl. Inst. Dent. Res., Bethesda, MD, 20892, USA

SO Brain Res. (1992), 585(1-2), 315-17

CODEN: BRREAP; ISSN: 0006-8993

DT Journal

LA English

AB Epidural and intrathecal administration of **opioids** to humans can produce facial **pruritus** and **scratching** that is naloxone reversible. It has been proposed that **opioids** may act at the level of the medulla to produce facial **pruritus** and assocd. **scratching** behavior. The effects of **.mu.**, **.delta.** and **.kappa. opioid-receptor agonists** microinjected unilaterally into the medullary dorsal horn (MDH) on facial **scratching** was investigated in cynomolgus monkeys. The selective **.mu. opioid-receptor agonist**, DAMGO (3.1-25.0 ng) produced large dose-dependent, naloxone-reversible increases in facial **scratches**. The selective **.delta. opioid-receptor agonist**, DPDPE (1.0-5.0 **.mu.g**) and the selective **.kappa. opioid-receptor agonist**, U-50,488H (0.1-5.0 **.mu.g**) did not produce significant increases in facial **scratching** behavior. Thus, the MDH is a site where DAMGO, a **.mu. opioid-receptor agonist**, can act to produce facial **scratching** in monkeys, and the MDH is likely to site where centrally administered **opioids** act to produce facial **pruritus** in humans.

L64 ANSWER 41 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1992:208091 HCAPLUS

DN 116:208091

TI Characterization of intrathecal vasopressin-induced antinociception, **scratching** behavior, and motor suppression

AU Thurston, Cindy L.; Campbell, Ian G.; Culhane, E. S.; Carstens, E.;
Watkins, L. R.
CS Dep. Anim. Physiol., Univ. California, Davis, CA, 95616, USA
SO Peptides (Fayetteville, N. Y.) (1992), 13(1), 17-25
CODEN: PPTDD5; ISSN: 0196-9781
DT Journal
LA English
AB Intrathecal (IT) administration of vasopressin (VP) produces antinociception, **scratching** behavior, and motor suppression. The present expts. characterized these effects with regards to the following: (1) VP **receptor** specificity, (2) possible involvement of endogenous **opiates**, (3) possible involvement of seizure activity, and (4) whether the antinociception is due to direct actions of VP at the spinal cord. These studies showed that IT administration of a V1-specific vasopressin antagonist completely blocked the antinociception, **scratching** behavior, and motor suppression produced by 25 ng IT vasopressin. Furthermore, IT administration of the vasopressin metabolite, [pGlu4,Cyt6]AVP(4-9), produced none of the effects produced by vasopressin. Systemic administration of the **opiate** antagonists naloxone (1 mg/kg i.p.) and naltrexone (10 mg/kg i.p.) had no significant effect on the antinociception produced by IT vasopressin, whereas naltrexone potentiated the **scratching** behavior. Neither the IT vasopressin-induced antinociception nor **scratching** behavior was affected by pretreatment with the anticonvulsant sodium valproate. In addn., IT vasopressin inhibited the tail flick reflex in rats with transected spinal cords, demonstrating direct spinal effects of vasopressin. In conclusion, IT administration of vasopressin produces antinociception, **scratching** behavior, and motor suppression via activation of VP-specific **receptors** in the spinal cord.

L64 ANSWER 42 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1992:51930 HCAPLUS
DN 116:51930
TI Neuromedin-induced excessive grooming/**scratching** behavior is suppressed by naloxone, neurotensin and a dopamine D1 receptor antagonist
AU Van Wimersma Greidanus, Tjeerd B.; Maigret, Carla
CS Rudolf Magnus Inst., Univ. Utrecht, Utrecht, 3521 GD, Neth.
SO Eur. J. Pharmacol. (1991), 209(1-2), 57-61
CODEN: EJPHAZ; ISSN: 0014-2999
DT Journal
LA English
AB Neuromedin B and neuromedin C were tested for their grooming/**scratching**-inducing effects and the compn. of neuromedin-induced grooming was established by calcg. the relative contribution of various grooming elements to the total grooming scores. Excessive grooming induced by neuromedins is characterized by a predominant display of **scratching**. Since neuromedin C is much more potent than neuromedin B in inducing excessive grooming/**scratching** behavior, it is concluded that the carboxyl-terminal heptapeptide of neuromedin C is important for this effect. Furthermore, it is concluded that dopamine D1 **receptors** and **opiate receptors** are involved in this effect since the dopamine D1 **receptor** antagonist, SCH 23390, as well as the **opiate receptor** antagonist, naloxone, suppresses or attenuates neuromedin C-induced excessive grooming/**scratching** behavior.

L64 ANSWER 43 OF 50 HCAPLUS COPYRIGHT 2002 ACS
AN 1991:422621 HCAPLUS
DN 115:22621
TI **.kappa.- And .delta.-opioids block sympathetically dependent hyperalgesia**
AU Taiwo, Yetunde O.; Levine, Jon D.
CS Dep. Anat. Med., Univ. California, San Francisco, CA, 94143-0724, USA
SO J. Neurosci. (1991), 11(4), 928-32
CODEN: JNRSDS; ISSN: 0270-6474
DT Journal

LA English
 AB Direct hyperalgesia induced by PGE2 can be blocked by .mu.- but not .delta.- or .kappa.-opioids. However, there is evidence that .kappa.- and .delta.-opioid **receptors** are located on sympathetic postganglionic neuron (SPGN) terminals, which mediate bradykinin (BK) hyperalgesia via SPGN-terminal-dependent prodn. of PGE2. Therefore, the antinociceptive effects of .delta.- and .kappa.-opioids on BK hyperalgesia were evaluated. It was demonstrated that the mech. hyperalgesia induced by intradermal injection of BK can be blocked by the .kappa.-opioid agonist U 50,488H and by the .delta.-opioid agonist (D-Pen2,5)-enkephalin (DPDPE), as well as the .mu.-opioid agonist Tyr-D-Ala-Gly-NMe-Phe-Gly-ol (DAMGO). Pertussis toxin prevented the inhibition of BK-induced hyperalgesia by U 50,488H, DPDPE, or DAMGO. The obsd. peripheral analgesic effects of .kappa.- and .delta.-opioid agonists result from actions upon SPGN terminals and these effects are mediated by inhibitory G-proteins.

L64 ANSWER 44 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1990:132682 HCAPLUS

DN 112:132682

TI **Opioid** inhibition of kainic acid-induced **scratching**: mediation by mu and sigma but not delta and **kappa receptors**

AU Kellstein, David E.; Coghill, Robert C.; Frenk, Hanan; Bossut, Daniel F.; Mayer, David J.

CS Med. Coll. Virginia, Virginia Commonw. Univ., Richmond, VA, 23298, USA

SO Pharmacol., Biochem. Behav. (1990), 35(1), 1-5

CODEN: PBBHAU; ISSN: 0091-3057

DT Journal

LA English

AB **Scratching** induced by intrathecal (IT) administration of kainic acid (0.5 nmol) to rats was inhibited by IT pretreatment with the selective .mu. **agonists** levorphanol (30 and 90 nmol), [D-Ala2,N-Met-Phe4,Gly5-ol]-enkephalin (DAGO) (0.4 and 1.1 nmol), or morphine (90 nmol), the mixed .mu.-.delta. **agonist** [D-Ala2,D-Leu5]-enkephalinamide (DADLE) (10 and 30 nmol), or the .sigma./phencyclidine (PCP) **agonists** dextrorphan (90 nmol) or (+)-N-allyl-N-normetazocine ([+]-NAM) (90 nmol). The .kappa. **agonists** dynorphin (1.1 nmol) and ethylketocyclazocine (90 nmol) had no significant effect, nor did the selective .delta. **agonist** [D-Pen2,D-Pen5]-enkephalinamide (DPDPE) (90 nmol). The nonopioids (+)-3-(3-hydroxyphenyl)-N-(1-propyl)piperidine ([+]-3-PPP, 90 nmol) and PCP (90 nmol), selective for .sigma. and PCP sites, resp., both antagonized kainic-induced **scratching**. Levorphanol- and DADLE-induced attenuation of **scratching** was partially antagonized by naltrexone. These findings suggest that **opioid** inhibition of kainic acid-induced **scratching** is mediated by classical .mu. **receptors** as well as .sigma. and PCP sites.

L64 ANSWER 45 OF 50 HCAPLUS COPYRIGHT 2002 ACS

AN 1989:51239 HCAPLUS

DN 110:51239

TI Intrathecal **injection** of a .kappa. **opioid agonist** produces hyperalgesia in the guinea pig

AU Leighton, G. E.; Hill, R. G.; Hughes, J.

CS Parke-Davis Res. Unit., Addenbrookes Hosp., Cambridge, UK

SO Eur. J. Pharmacol. (1988), 157(2-3), 241-2

CODEN: EJPHAZ; ISSN: 0014-2999

DT Journal

LA English

AB The .kappa.-opioid agonist U-69593 at 30 .mu.g intrathecally in the lumbar region reduced the nociceptive threshold in guinea pigs in a paw-pressure test. This effect was seen in 5 min, peaked at 15 min, and was gone by 30 min. Pretreatment with naloxone

abolished this hyperalgesia.

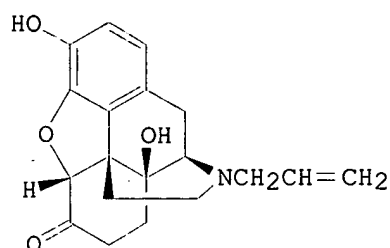
L64 ANSWER 46 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1987:13014 HCAPLUS
 DN 106:13014
 TI **Itch** and endorphins
 AU Haegermark, O.
 CS Dep. Dermatol., Karolinska Sjukhuset, Stockholm, 104 01, Swed.
 SO New Trends Allergy 2, [Pap. Int. Symp.] (1986), Meeting Date
 1985, 128-34. Editor(s): Ring, Johannes; Burg, Guenter. Publisher:
 Springer, Berlin, Fed. Rep. Ger.
 CODEN: 55GXAT
 DT Conference; General Review
 LA English
 AB A review, with 26 refs., on the involvement of endorphin [60118-07-2]s
 and **opiate receptors** in the transmission of
pruritis both at peripheral and central levels and on the
itch-relieving effects of naloxone.

L64 ANSWER 47 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1986:179629 HCAPLUS
 DN 104:179629
 TI In **vivo studies** on **kappa opioid**
receptors
 AU Cowan, Alan; Gmerek, Debra E.
 CS Sch. Med., Temple Univ., Philadelphia, PA, 19140, USA
 SO Trends Pharmacol. Sci. (1986), 7(2), 69-72
 CODEN: TPHSDY; ISSN: 0165-6147
 DT Journal; General Review
 LA English
 AB Various in vivo tests for the screening of agents with **.kappa.-**
opioid activity are surveyed. Special emphasis is placed on a
 bombesin [31362-50-2]-induced **scratch** test in rats; other
 procedures include diuresis and increased food intake in rats and
 nalorphine discrimination and morphine withdrawal in monkeys. These tests
 are designed to assist in the optimization of the activity of
opioid analgesics at the various **opioid**
receptors.

L64 ANSWER 48 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1986:62438 HCAPLUS
 DN 104:62438
 TI Hyperalgesia mediated by **peripheral opiate**
receptors in the rat
 AU Van der Kooy, Derek; Nagy, James I.
 CS Dep. Anat., Univ. Toronto, Toronto, ON, M5S 1A8, Can.
 SO Behav. Brain Res. (1985), 17(3), 203-11
 CODEN: BBREDI; ISSN: 0166-4328
 DT Journal
 LA English
 AB The responses of rats to noxious chem. stimuli applied to the ear (ear
scratch test) were measured after local pretreatment of these
 areas with etorphine [14521-96-1]. Local etorphine administration
 produced a low-dose hyperalgesia and high-dose analgesia. Local as
 opposed to systemic effects of etorphine were inferred from the absence of
 effects on the contralateral vehicle-treated ear. Systemic administration
 of naloxone or of a quaternary **opiate** antagonist (MRZ 2663-BR),
 which is relatively ineffective in crossing the blood-brain barrier,
 blocked the low-dose hyperalgesic effect of etorphine in the ear
scratch test. As a test for the putative hyperalgesic function of
 peripheral sensory nerve **opiate receptors**, neonatal
 rats were treated with capsaicin (50 mg/kg s.c.) to destroy specifically
 the subpopulation of primary sensory neurons on which the peripheral
opiate receptors are thought to be located, without
 markedly altering pain thresholds. As adults, these neonatally treated
 rats showed potentiated analgesic responses to systemic morphine

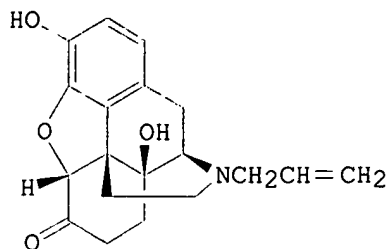
[57-27-2], as would be predicted by central analgesic **opiate receptors** now acting without opposition from peripheral hyperalgesic **opiate receptors**. Thus, **opiate receptors** on primary sensory neurons may mediate hyperalgesic functions, and endogenous **opioids** might normally play a role in the peripheral induction of irritation, inflammation, and pain reactions.

L64 ANSWER 49 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1982:608198 HCAPLUS
 DN 97:208198
 TI Behavioral alterations produced by chronic naloxone **injections**
 AU Malin, David H.; Layng, Michael P.; Swank, Paul; Baker, Melanie J.; Hood, Joyce L.
 CS Univ. Houston, Houston, TX, 77058, USA
 SO Pharmacol., Biochem. Behav. (1982), 17(3), 389-92
 CODEN: PBBHAU; ISSN: 0091-3057
 DT Journal
 LA English
 GI



AB Repeated blockade of the endorphin **receptors** by naloxone (I) [465-65-6] (0.6 mg/kg twice daily for 6 days, s.c.) eventually induces symptoms resembling an **opiate** abstinence syndrome, despite the complete absence of **opiate** narcotics. Body shakes, head shakes, **scratches** and total symptoms were significantly elevated after I treatment. Symptoms were completely reversed by a small dose of morphine [57-27-2] but not by naloxone. In a 2nd expt., rats were injected for 10 days with the same dosage of naloxone. The abstinence-like syndrome began after 6 days of naloxone and continued for several days after cessation of injections. Total symptoms, body shakes, **scratches** and aggression were significantly elevated over controls and were reversed by morphine but not by naloxone.

L64 ANSWER 50 OF 50 HCAPLUS COPYRIGHT 2002 ACS
 AN 1982:97588 HCAPLUS
 DN 96:97588
 TI **Antipruritic** effect of an opiate antagonist, naloxone hydrochloride
 AU Bernstein, Joel E.; Swift, Robert M.; Soltani, Keyoumars; Lorincz, Allan L.
 CS Pritzker Sch. Med., Univ. Chicago, Chicago, IL, USA
 SO J. Invest. Dermatol. (1982), 78(1), 82-3
 CODEN: JIDEAE; ISSN: 0022-202X
 DT Journal
 LA English
 GI



AB Central elicitation of **itch** by morphine [57-27-2] may result from binding to **opiate receptors**, mimicking the physiol. binding of endorphins and enkephalins to these **receptors**. Pretreatment of normal subjects with naloxone (I) [465-65-6] resulted in a diminution or abolition of histamine-provoked **itch**. Apparently, central **opioid** peptides are mediators of the **itch** sensation. Naloxone and related **opiate** antagonists may be useful in the treatment of various **pruritic** disorders.

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L90 ANSWER 1 OF 1 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

AN 92254270 EMBASE

DN 1992254270

TI Effects of central administration of **opioids** on **facial scratching** in monkeys.

AU Thomas D.A.; Williams G.M.; Iwata K.; Kenshalo Jr. D.R.; Dubner R.

CS Neurobiology/Anesthesiology Branch, National Inst. of Dental Research, National Institutes of Health, Bethesda, MD 20892, United States

SO Brain Research, (1992) 585/1-2 (315-317).

ISSN: 0006-8993 CODEN: BRREAP

CY Netherlands

DT Journal; Article

FS 030 Pharmacology

037 Drug Literature Index

LA English

SL English

AB Epidural and intrathecal administration of **opioids** to humans can produce facial **pruritus** and **scratching** that is naloxone reversible. It has been proposed that **opioids** may act at the level of the medulla to produce facial **pruritus** and associated **scratching** behavior. We investigated the effects of .mu., .delta. and .kappa. **opioid-receptor agonists** microinjected unilaterally into the medullary dorsal horn (MDH) on **facial scratching** in cynomolgus monkeys. The selective .mu. **opioid-receptor agonist**, DAMGO (3.1-25.0 ng) produced large dose-dependent, naloxone-reversible increases in facial **scratches**. The selective .delta. **opioid-receptor agonist**, DPDPE (1.0-5.0 .mu.g) and the selective .kappa. **opioid-receptor agonist**, U-50,488H (0.1-5.0 .mu.g) did not produce significant

increases in **facial scratching** behavior. We conclude that the MDH is a site where DAMGO, a .mu. **opioid-receptor agonist**, can act to produce **facial scratching** in monkeys, and that the MDH is likely the site where centrally administered **opioids** act to produce **facial pruritus** in humans.

CT Medical Descriptors:

*brain stem

***pruritus**

animal experiment

article

controlled study

dose response

intracerebral drug administration

male

monkey

nonhuman

priority journal

regional perfusion

Drug Descriptors:

***opiate receptor**

***receptor subtype**

*3,4 dichloro n methyl n [2 (1 pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate: PD, pharmacology

*3,4 dichloro n methyl n [2 (1 pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate: CM, drug comparison

*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: PD, pharmacology

*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: IT, drug interaction

*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: CB, drug combination

*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: DO, drug dose

*enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]: CM, drug comparison

*enkephalin[2,5 dextro penicillamine]: PD, pharmacology

*enkephalin[2,5 dextro penicillamine]: CM, drug comparison

naloxone: IT, drug interaction

naloxone: CB, drug combination

RN (3,4 dichloro n methyl n [2 (1 pyrrolidinyl)cyclohexyl]benzeneacetamide methanesulfonate) 83913-06-8; (enkephalin[2 dextro alanine 4 methylphenylalanine 5 glycine]) 78123-71-4; (enkephalin[2,5 dextro penicillamine]) 88373-73-3, 88381-29-7; (naloxone) 357-08-4, 465-65-6

CN U 50488h

CO Sigma (United States)

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FILE 'WPIX' ENTERED AT 10:14:53 ON 18 JAN 2002

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L108 ANSWER 1 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-599819 [68] WPIX

DNC C2001-177425

TI New **itching** inhibitor containing morphinan derivative for cornea or conjunctiva.

DC B02

PA (TORA) TORAY IND INC

CYC 1

PI JP 2001163784 A 20010619 (200168)* 13p A61K031-485

ADT JP 2001163784 A JP 1999-345898 19991206

PRAI JP 1999-345898 19991206

IC ICM A61K031-485

ICS A61P027-02

ICA C07D489-08

AB JP2001163784 A UPAB: 20011121

NOVELTY - New **itching** inhibitor for cornea or conjunctiva comprises morphinan derivative or its pharmacologically acceptable acid salts as active ingredient.

DETAILED DESCRIPTION - New **itching** inhibitor for cornea or conjunctiva comprises morphinan derivative of formula (I) or its pharmacologically acceptable acid salts as active ingredient.

... = double or single bond;

R1 = 1-5C alkyl, 4-7C cycloalkyl, 5-7C cycloalkenylalkyl, 6-12C aryl, 7-13C aralkyl, 4-7C alkenyl, allyl, 1-5C furan-2-alkyl or 1-5C thiophenyl-2-alkyl;

R2 = H, OH, NO₂, 1-5C alkanoyloxy, 1-5C alkoxy, 1-5C alkyl or -NR₉R₁₀;

R3 = H, hydroxy, 1-5C alkanoyloxy, 1-5C alkoxy;

R9 = H or 1-5C alkyl;

R10 = H, 1-5C alkyl or C(O)R₁₁;

R11 = H, phenyl or 1-5C alkyl;

A = -XC(=Y)-, -XC(=Y)Z-, -X- or -XS₂-;

X, Y or Z = NR₄, S or O;

R4 = H, 1-5C alkyl, 6-12C aryl;

B = valence bond, 1-14C alkylene (optionally substituted with 1-5C alkoxy, 1-5C alkanoyloxy, hydroxy, F, Cl, BR. I, amino, NO₂, CN, CF₃ or phenoxy and 1-3 methylenes can be placed by carbonyl), 2-14C acyclic unsaturated hydrocarbon having 1 to 3 double bond and/or triple bond, thioether bond, 1-14C hydrocarbon having 1 to 5 ether bond and/or amino bond;

R5 = H or phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl, isoquinolinyl or a group of formula (i)-(iv);

Q = N, O or S;

T = CH, N, O or S;

I = 0-5;

m, n = 0-5; and

m+n = 0-5;

R6 = H;

R7 = H, hydroxy, 1-5C alkoxy or 1-5C alkanoyloxy;

R6 + R7 = -O-, -CH₂- or -S-;

R8 = H, 1-5C alkyl or 1-5C alkanoyl.

An INDEPENDENT CLAIM is also included for **itching** inhibitor for cornea or conjunctiva comprising morphinan quaternary ammonium derivative of formula (II) or morphinan-N-oxide derivative of formula (III) or its acid salts as active ingredient.

R1 = 1-5C alkyl, 4-7C cycloalkyl, 5-7C cycloalkenylalkyl, 7-13C aralkyl, 4-7C alkenyl, allyl, preferably methyl, ethyl, propyl, butyl, isobutyl, cyclopropylmethyl, allyl, benzyl or phenethyl;

R2 = H, OH, NO₂, 1-5C alkanoyloxy, 1-5C alkoxy, 1-5C alkyl, preferably H, OH, acetoxy or methoxy;

R3 = H, hydroxy, 1-5C alkanoyloxy, 1-5C alkoxy, preferably H, OH, acetoxy or methoxy;

R4 = H, 1-5C alkyl, 6-12C aryl, preferably H or 1-5C alkyl;
A = 1-6C alkylene, C=C, C equivalent to C;
R5 = H or phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl,
isoquinolinyl or a group of formula (i)-(iv), preferably phenyl or (i);
X = counter ion.

ACTIVITY - Antipruritic; Ophthalmological.

MECHANISM OF ACTION - Opioid kappa receptor agonist.

(-)-17-(Cyclopropylmethyl)-3,14- beta -dihydroxy-4,5- alpha -epoxy-6-
beta -(N-methyl-trans-3-(3- furyl)acrylamide)morphinan hydrochloride of
formula (Ia) was dissolved in saline to prepare 0.1 micro gram/ml
solution. The obtained solution (20 ml) (2 mg/site) was administered on
the right eye of Hartley guinea pig. 30 minutes later, histamine solution
(5 mg/site) was administered on the right eye, and saline (20 ml) was
administered on the left eye. For the next 30 minutes, guinea pig was
filmed by a video camera to observe its scratching activity. The results
showed that the compound (29) significantly inhibited itching induced by
histamine.

USE - Itching inhibitor is used for the treatment of itching caused
by corneal ulcer, bacterial keratitis, viral keratitis, keratomycosis,
lamellar keratitis, xerophthalmia, dry eye, keratoconjunctivitis sicca,
infectious keratoconjunctivitis, allergic conjunctivitis, vernal
conjunctivitis, phlyctenular conjunctivitis, follicular conjunctivitis,
conjunctivitis of Stevens-Johnson syndrome, conjunctivitis of pemphigoid,
dacryocystitis or hordeolum.

ADVANTAGE - The inhibitor is effective for reducing itching due to
its opioid kappa receptor agonistic compound.

Dwg.0/1

FS CPI
FA AB; GI; DCN
MC CPI: B06-D03; B06-H; B14-N03; B14-N17

L108 ANSWER 2 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-441332 [47] WPIX

DNN N2001-326505 DNC C2001-133243

TI New metalloptides which are specific for **opioid**
receptors, are useful in treatment of e.g. pain, drug addiction,
autoimmune disorders or inflammation, or for appetite suppression.

DC B04 P34

IN HUI-ZHI, C; SHARMA, S D; WEI, Y

PA (PALA-N) PALATIN TECHNOLOGIES INC

CYC 94

PI WO 2001036006 A1 20010525 (200147)* EN 52p A61K051-00

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ
NL OA PT SD SE SL SZ TR TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM
DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC
LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE
SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001016238 A 20010530 (200152) A61K051-00

ADT WO 2001036006 A1 WO 2000-US31797 20001117; AU 2001016238 A AU 2001-16238
20001117

FDT AU 2001016238 A Based on WO 200136006

PRAI US 1999-166582P 19991119

IC ICM A61K051-00

ICS A61M036-14

AB WO 200136006 A UPAB: 20011129

NOVELTY - Peptides, and libraries of these, which include a metal
ion-binding domain (MIBD), and which are specific for **opioid**
receptors when complexed with a metal ion, are described.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a construct comprising a MIBD comprising two or more linked amino
acid residues (AARs) which form a nitrogen-containing and
sulfur-containing ligand available for complexing with a metal ion. The
construct is conformationally restrained in a structure which is specific
for one or more **opioid receptors** upon complexing the
MIBD with a metal ion;

(2) a manufactured peptide, and its salts, which comprises a MIBD comprising two or more contiguous amino acids and a determined biological-function domain (BFD) specific for one or more **opioid receptors**. At least a portion of the BFD is co-extensive with at least a portion of the MIBD. The BFD is conformationally restrained upon complexing the MIBD with a metal ion;

(3) a combinatorial library targeted to **opioid receptors** of different sequence peptide members or peptidomimetic sequence synthesized on a solid phase (SP), where each library member comprises a peptide sequence or peptidomimetic sequence of 3 or more AARs (and/or mimics of these) bound to the SP. This sequence comprises (a) a sequence of 2 or more AARs (and/or mimics) which form a MIBD and which include at least one amino acid residue (and/or mimic) containing at least one S atom which is protected by an orthogonal S-protecting group; (b) a sequence of one or more AARs (and/or mimics) at the N- and/or C-terminus of the MIBD; and (c) a cleavable bond which attaches the sequence to the SP. The S-protecting group can be removed without cleaving the sequence from the SP;

(4) a combinatorial library targeted to **opioid receptors** of different sequence peptide members or peptidomimetic sequence synthesized in solution, where each library member comprises a peptide sequence or peptidomimetic sequence of 3 or more AARs (and/or mimics of these) bound to an SP. This sequence comprises (a) a sequence of 2 or more AARs (and/or mimics) which form a MIBD and which include at least one amino acid residue (and/or mimic) containing at least one S atom which is protected by an orthogonal S-protecting group; and (b) a sequence of one or more AARs (and/or mimics) at the N- and/or C-terminus of the MIBD; and

(5) metallopeptides, or their salts, of formula (I)-(VII), each complexed to a metal ion. R1-R2-R3-R4 (I), R5-R2-R6-R3-R7 (II), R5-R8-R2-R6-R3-R7 (III), R9-R1-R3-R10 (IV), R5-R11-R6-R12 (V), R5-R11-R13-R3-R10 (VI) or R14-R6-R15-R3-R16 (VII).

R1 = an L- or D-amino acid with a phenol moiety side chain and with an N atom available for complexation to a metal ion;

R2 = a neutral or basic L- or D-amino acid with an N atom available for complexation to a metal ion;

R3 = L- or D-Cys, L- or D-homoCys, L- or D-Pen, or a derivative or homologue of any of these, with both an N atoms and SH group available for complexation to a metal ion;

R4 = an L- or D-amino acid with a neutral aromatic side chain or a side chain with an aromatic ring substituted by halogen, nitro or and alkyl group; or a des-carboxyl derivative corresponding to such and L- or D-amino acid;

R5 = an L- or D-amino acid with a phenol moiety side chain, excluding des-carboxy derivatives;

R6 = an L- or D-amino acid with a neutral side chain or a side chain with an aromatic ring substituted by halogen, nitro or alkyl group, and with an N atom available for complexation to a metal ion;

R7 = a free carboxylate or terminal amide of R3 or a neutral or basic L- or D-amino acid, or a des-carboxyl derivative corresponding to such an L- or D-amino acid;

R8 = a neutral or basic L- or D-alpha or-omega amino acid, or a derivative of this;

R9 = an L- or D-amino acid with a basic functional group side chain, and with an N atom available for complexation to a metal ion;

R10 = a free carboxylate, primary amide or aryl or aralkyl chain substituted amide derivative of R3, or an L- or D-amino acid with a neutral aromatic side chain or side chain with a ring substituted by halogen, nitro or an alkyl group;

R11 = L- or D-Cys, L- or D-homoCys, L- or D-Pen, or a derivative or homologue of these, with an SH group available for complexation to a metal ion;

R12 = a neutral L- or D-amino acid with an N atom available for complexation to a metal ion, and with a terminal amide with an N atom available for complexation to a metal ion;

R13 = an L- or D-amino acid with a neutral aliphatic or aromatic side

chain or side chain with a ring substituted by halogen, nitro or an alkyl group, and which has an N atom available for complexation to a metal ion;

R14 = a neutral or basic L- or D-alpha or -omega amino acid, or a derivative of this, excluding higher omega-amino aliphatic carboxylic acid homologues;

R15 = a L- or D-amino acid with an N atom available for complexation to a metal ion and hydrogen bond forming groups in the side chain;

R16 = an L- or D-amino acid with a phenol moiety side chain, including des-carboxy derivatives.

ACTIVITY - Analgesic; immunomodulator; antiinflammatory; neuroleptic; tranquilizer; anorectic.

MECHANISM OF ACTION - **Opioid receptor agonist; opioid receptor antagonist.**

USE - The materials described above are **agonists**, antagonists or mixed **agonist/antagonists** of **opioid receptors**, including mu -, delta - and **kappa-opiate receptors**. They can be used in treatment of pain and may be used to treat various addictions (including morphine, alcohol or cocaine addiction). They may also be useful in treatment of autoimmune diseases, inflammation, **pruritus**, irritable bowel syndrome, psychotic disorders or gastrointestinal disorders. They may also be used to suppress appetite.

ADVANTAGE - The above peptides are substantially more specific for one or more **opioid receptors** when complexed with a metal than when not complexed with a metal ion. They are less susceptible to degradation by proteases and other enzymes than are conventional peptides, and are suitable for administration by means other than parenteral administration.

Dwg.0/0

FS CPI GMPI

FA AB; DCN

MC CPI: B04-C01; B05-A03; B14-C01; B14-C03; B14-E10; B14-E10C; B14-E12; B14-G02A; B14-G02D; B14-J01B3; B14-L01; B14-L06; B14-M01A; B14-M01C; B14-N17

TECH UPTX: 20010822

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: The peptides may be prepared using known peptide synthesis methods. The orthogonal S-protecting group is, e.g., S-thio-butyl, acetamidomethyl, 4-methoxytrityl, S-sulfonate or 3-nitro-2-pyridinesulfonyl.

L108 ANSWER 3 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-244295 [25] WPIX

DNC C2001-073269

TI Agents for treating neuropathic pain comprise morphinan derivative.

DC B02

IN ENDO, T; KAWAMURA, K; KURAISHI, Y; NAGASE, H; SHIRAKI, K; SUZUKI, T; TANAKA, T

PA (TORA) TORAY IND INC

CYC 22

PI WO 2001014383 A1 20010301 (200125)* JA 33p C07D489-06
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: CA CN JP US

ADT WO 2001014383 A1 WO 2000-JP5690 20000824

PRAI JP 1999-236778 19990824

IC ICM C07D489-06

ICS A61K031-4738; A61K031-485; A61K045-00; A61P025-04; C07D471-04; C07D489-08

AB WO 200114383 A UPAB: 20010508

NOVELTY - Agents for treating neuropathic pain comprise a morphinan derivative (I).

DETAILED DESCRIPTION - Agents for treating neuropathic pain comprise a morphinan derivative of formula (I) or its acid addition salt.

R1 = Alk (optionally substituted by furan-2-yl or thiophen-2-yl), 4-7C cycloalkylalkyl, 5-7C cycloalkenylalkyl, 6-12C aryl, 7-13C aralkyl, 4-7C alkenyl or allyl;

Alk = 1-5C alkyl;

R2 = H, OH, NO2, OCOAlk, OAlk, Alk or NR9R10;
R9 = H or Alk;
R10 = H, Alk or COR11;
R11 = H, phenyl or Alk;
R3 = H, OH, OCOAlk, or OAlk;
A = XC(=Y), XC(=Y)Z, X or XSO2;
X, Y, Z = NR4, S or O;
R4 = H, Alk or 6-12C aryl;
a = single or double bond;
B' = bond or 1-14C alkylene (optionally containing 1-3 unsaturated bonds, optionally substituted by 1 or more OAlk, OCOAlk, OH, F, Cl, Br, I, amino, NO2, CF3 or phenoxy, and optionally with 1-3 CH2 groups replaced by CO);
R5 = H or J;
J = phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl, isoquinolinyl, pyrrolyl, furanyl thiophenyl, indolyl, benzofuranyl, benzothiophenyl or Cyc all optionally substituted by 1 or more Alk, OAlk, OCOAlk, OH, F, Cl, Br, I, amino, NO2, CN, SCN, CF3, OCF3 or methylenedioxy;
Cyc = 3-8C cycloalkyl or 3-8C cycloalkenyl both with optionally with one CH2 replaced by NH, S or O;
R6, R7 = H, OH, OAlk or OCOAlk; or
R6+R7 = O, CH2 or S; and
R8 = H, Alk or COAlk.
N.B. b has not a definition.
INDEPENDENT CLAIMS are also included for:
(1) an animal model for neuropathic pain comprising administering (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-transquinolino(2,3-g)isoquinoline to the animal; and
(2) compounds for treating neuropathic pain obtained using the above model.

ACTIVITY - Analgesic. In a (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-transquinolino(2,3-g)isoquinoline induced neuropathic pain model in mice (-)-17-cyclopropyl-3,14 beta -dihydroxy-4,5 alpha -epoxy-6 beta -(N-methyl-trans-3-(3-furyl)acrylamido)morphinan hydrochloride at 0.056 mg/kg significantly reduced **scratching** biting and licking.

MECHANISM OF ACTION - **Kappa opioid receptor agonists.**

USE - (I) are useful as **kappa opioid receptor agonists** useful for treating neuropathic pain e.g. causalgia and pain due to diabetes, alcohol or other toxicities, amyloidosis, viral infections, trigeminal headaches, post-herpes zoster neuralgia, cerebral fibrosis, fevers, AIDS, multiple sclerosis and Alzheimer's disease.

Dwg.0/8

FS CPI
FA AB; GI; DCN
MC CPI: B04-A04; B14-C01

L108 ANSWER 4 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-234235 [24] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27]; 2000-349606 [29]; 2001-440271 [38]

DNC C2001-070038

TI Prevention or treatment of **pruritus**, caused by e.g. anaphylactic reaction, enterobiasis or asteatotic eczema comprises administering a composition comprising N-(2-aminocyclohexyl)-N-methyl-phenylalkanoamide derivatives.

DC A23 A96 B03

IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 1

PI US 6180623 B1 20010130 (200124)* 71p A61K031-337

ADT US 6180623 B1 CIP of US 1996-612680 19960308, CIP of US 1997-796078

19970205, Div ex US 1997-891833 19970714, Div ex US 1998-45522 19980321,
Div ex US 1999-307517 19990507, US 1999-436057 19991108
FDT US 6180623 B1 CIP of US 5646151, CIP of US 5688955, Div ex US 5763445, Div
ex US 5981513, Div ex US 6028063
PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078
19970205; US 1998-45522 19980321; US 1999-307517 19990507; US
1999-436057 19991108
IC ICM A61K031-337
ICS A61K031-535; C07D273-08
AB US 6180623 B UPAB: 20010822

NOVELTY - Prevention or treatment of **pruritus** comprises
administering a composition comprising a N-(2-aminocyclohexyl)-N-methyl-
phenylalkanoamide derivative (I) or its salt.

DETAILED DESCRIPTION - Prevention or treatment of **pruritus**
comprises administering a composition comprising a compound of formula (I)
or a salt of (I), other than (plus or minus)-trans-3,4-dichloro-N-methyl-
N-(2-dimethylaminocyclohexyl)-phenylacetamide hydrochloride and (plus or
minus)-trans-3,4-dichloro-N-methyl-N-(2-pyrrolidinocyclohexyl)-
phenylacetamide hydrochloride, in a vehicle.

n = 1-3;

R1, R2 = CH3, (CH2)m, CH2CH(OH)CH2CH2, CH2CH(F)CH2CH2, (CH2)2O(CH2)2
or (CH2)2CH=CHCH2;

m = 4-8;

R3, R4 = H, OCH3, alkyl, or -O(CH2)2;

X9 = (a) 1-4 of halo, CF3, OCH3, SO2NH(CH2)qCOOH, NH2, NHSO2CH3,
NHP(O)(OBn)2, NHP(O)(OH)2, NH(CH2)qCOOH, SO2CH3, OP(O)(OBn)2, OP(O)(OH)2,
COOH, O(CH2)qCOOH, O(CH2)qSO3H and O(CH2)qOPO3H2 or (b) a group of formula
(i)-(iii):

q = 1-20;

t = 1-20;

R5 = H or CH3C(O)-; and

X6 = CO2H, NHSO2CH3, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or
OP(O)(OH)2;

Provided that the compound of formula (I) is not (+ or
-)-trans-3,4-dichloro-N-methyl-N-(2-(dimethylamino)cyclohexyl)-
phenylacetamido hydrochloride or (+ or -)-trans-3,4-dichloro-N-methyl-N-(2-
(1-pyrrolidinyl)cyclohexyl)-phenylacetamido hydrochloride or their salts.

ACTIVITY - Analgesic; anti-hyperalgesic; **antipruritic**;
antithyroid.

Testing was performed in a **scratch** mouse model. 100
microliters of the vehicle 20% v/v cremaphor EL (3-5 doses) was injected
subcutaneously into the backs of the necks of mice 20 minutes before
challenging them with 100 microliters of Compound 48/80 (shown to produce
an **itching** sensation in humans) (2 micrograms/ml, 50 micrograms)
which was also injected subcutaneously into the backs of the necks of the
mice. One minute later the mice were observed for 30 minutes and the
number of hind leg **scratching** movements directed at the neck
recorded. The vehicle-injected mice **scratched** 79 plus or minus
16 times in the 30 minutes after being challenged with Compound 48/80.
Then, various doses of the compounds to be tested for **antipruritic**
activity were administered subcutaneously to the backs of the necks of the
mice. One minute after administration, the mice were again observed for 30
minutes and the number of hind leg **scratching** movements recorded
as before. The means values for **scratching** were normalized to
relative percentage antagonism of **scratching** and then plotted
versus the dose of test compounds. Interval estimates of mean A50 were
determined by non-linear regression analysis and the mean % inhibition of
scratching calculated. The compounds tested showed dose-dependent
activity in the range from 15-95% based upon subcutaneous doses of
0.5-10.0 mg/kg.

MECHANISM OF ACTION - (I) are **kappa opioid**
receptor agonists.

USE - For preventing or treating **pruritus**, especially
caused by anaphylactic reaction, urticaria, chiggers, secondary
hyperparathyroidism, cutaneous larva migrans, dermal myiasis,
onchocerciasis, pediculosis, enterobiasis, schistosome dermatitis or

asteatotic eczema.

ADVANTAGE - (I) are substantially devoid of CNS (central nervous system) effects.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: A12-V01; B07-D03; B10-B01B; B10-B02B; B14-B02; B14-G02; B14-G02A; B14-G02B; B14-L01; B14-N11; B14-N17

TECH UPTX: 20010502

TECHNOLOGY FOCUS - PHARMACEUTICALS - The composition comprises 0.1-50% w/w of (I).

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preparation: (I) are prepared e.g. by:

- (1) reaction of cyclohexene oxide with pyrrolidine to give the alcohol derivative of formula (II);
- (2) conversion of (II) to a methane sulfonate derivative of formula (III);
- (3) reaction of (III) with methylamine to give (plus or minus)-trans-2-pyrrolidiny-N-methylcyclohexylamine of formula (IV);
- (4) coupling of (IV) with various aryl acetic acids in the presence of N,N-dicyclohexylcarbodiimide and pyridine to produce the desired arylacetamides of formula (V); and
- (5) addition of a 1M etherial hydrochloric acid to (V) to give the hydrochloride salts of (V).

L108 ANSWER 5 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2001-090169 [10] WPIX

CR 1998-332207 [29]; 1999-131835 [11]; 1999-152855 [13]; 2000-072070 [06]; 2000-316903 [25]

DNC C2001-026321

TI Anti-pruritic pharmaceutical formulations comprise **kappa agonist** compounds.

DC B02

IN CHANG, A; COWAN, A; FARRAR, J J; KUMAR, V; ZHANG, W Y

PA (APOL-N) APOLOR CORP

CYC 1

PI US 6156769 A 20001205 (200110)* 20p A61K031-445

ADT US 6156769 A Div ex US 1997-892599 19970714, Div ex US 1998-64695 19980422, Div ex US 1998-184393 19981102, Div ex US 1999-411111 19991004, US 2000-488420 20000120

FDT US 6156769 A Div ex US 5760023, Div ex US 5869521, Div ex US 6004694, Div ex US 6048860

PRAI US 1997-892599 19970714; US 1998-64695 19980422; US 1998-184393 19981102; US 1999-411111 19991004; US 2000-488420 20000120

IC ICM A61K031-445

AB US 6156769 A UPAB: 20010220

NOVELTY - **Pruritus** in a mammal is prevented or treated by administering tetracyclic derivatives (I) as **kappa agonists**.

DETAILED DESCRIPTION - **Pruritus** in a mammal is prevented or treated by administering tetracyclic derivatives of formula (I) or their salts as **kappa agonists**.

a = single or double bond;

R1 = 1-5C alkyl, 4-7C cycloalkyl, 5-7C cycloalkenylalkyl, 6-12C aryl, 7-13C aralkyl, 4-7C alkenyl, allyl, furan-2-yl(1-5C)alkyl or thiophen-2-yl(1-5C)alkyl;

R2 = H, OH, NO2, 1-5C alkanoyloxy, 1-5C alkoxy or NR9R10;

R9 = H or 1-5C alkyl;

R10 = H, 1-5C alkyl or -C(=O)R11;

R11 = H, phenyl or 1-5C alkyl;

R3 = H, OH, 1-5C alkanoyloxy or 1-5C alkyl;

A = -XC(=Y)-, -XC(=Y)Z-, -X-, -XSO2- or -OC(OR4)R4-;

X, Y, Z = NR4, S or O;

R4 = H, 1-5C alkyl or 6-12C aryl;

B' = valence bond, alkylene group having 1-14C and optionally substituted with 1-5C alkoxy, 1-5C alkanoyloxy, OH, F, Cl, Br, I, NH2,

NO₂, CN, CF₃ or phenoxy; 1 to 3 methylene groups may be replaced with CO, acyclic unsaturated hydrocarbon containing 1-3 double bonds and/or triple bonds and having 2-14C atoms which is optionally substituted with 1-5C alkoxy, 1-5C alkanoyloxy, OH, F, Cl, Br, I, NH₂, NO₂, CN, CF₃ or phenoxy and 1-3 methylene groups may be replaced with carbonyl, 1-14C hydrocarbon containing 1-5 thioether, ether and/or amino bonds, and when the hetero atoms are not bonded directly to A, 1-3 methylene groups may be replaced with carbonyl groups;

R₅ = H or organic group optionally substituted with 1-5C alkyl, 1-5C alkoxy, 1-5C alkanoyloxy, OH, F, Cl, Br, I, NH₂, NO₂, CN, isothiocyanate, CF₃ or methylenedioxy, phenyl, naphthyl, fluorenyl, pyridyl, quinolinyl, isoquinolinyl or a group of formula (i) to (iv);

Q = N, O or S;

T = CH, N, S or O;

i = 0-5;

m, n = greater than 0 and m + n = less than 5;

R₆ = H;

R₇ = H, OH, 1-5C alkoxy, 1-5C alkanoyloxy; or

R₆ + R₇ = -O-, -CH₂- or -S-; R₈ = H, 1-5C alkyl or 1-5C alkanoyl.

ACTIVITY - **Antipruritic**; analgesic. The **antipruritic** activity of the compounds were evaluated using mouse **scratch** model under blind conditions as specified. A specified compound showed a 72 % inhibition of **scratching** at a dose of 5 mg/kg sc.

MECHANISM OF ACTION - The compounds (I) are **kappa opioid agonists** and possess anti-**pruritic** and antihyperalgesic activity.

USE - The compounds are useful for preventing or treating **pruritus** in mammals.

ADVANTAGE - The compounds are devoid of central nervous system effects.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B04-A04; B14-N17

TECH UPTX: 20010220

TECHNOLOGY FOCUS - ORGANIC CHEMISTRY - Preferred Preparation: The compounds are prepared as described in various US4145435, US4359476, US4855316, and US5114945.

L108 ANSWER 6 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2000-349606 [30] WPIX

CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27]; 2001-234235 [13]; 2001-440271 [38]

DNC C2000-106280

TI Use of selected **opioid kappa receptor**

agonists with no action on the central nervous system to prevent or treat **pruritis**.

DC B03 B05

IN CHANG, A; GAUL, F; GUO, D; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 1

PI US 6057323 A 20000502 (200030)* 119p A61K031-495

ADT US 6057323 A Cont of US 1996-612680 19960308, Div ex US 1997-796078 19970205, Div ex US 1997-899086 19970723, CIP of US 1998-34661 19980303, CIP of US 1998-150369 19980909, US 1998-183011 19981030

FDT US 6057323 A Cont of US 5646151, Div ex US 5688955, Div ex US 5744458

PRAI US 1998-183011 19981030; US 1996-612680 19960308; US 1997-796078 19970205; US 1997-899086 19970723; US 1998-34661 19980303; US 1998-150369 19980909

IC ICM A61K031-495

ICS C07D241-04

AB US 6057323 A UPAB: 20010822

NOVELTY - The use of **opioid kappa receptor**

agonists (I) with no activity in the central nervous system to prevent or treat **pruritis** is new.

DETAILED DESCRIPTION - The prevention and treatment of **pruritis** with **Kappa agonists** of formula (I) and their salts is new.

$n = 3$;

$R_1, R_2 = CH_3$; or

$R_1 + R_2 = (CH_2)_m, CH_2CH(OH)(CH_2)_2, CH_2CH(F)(CH_2)_2, (CH_2)_{20}(CH_2)_2$ or $(CH_2)_2CH=CHCH_2$;

$m = 4-8$;

Ar_1 = phenyl optionally substituted with 1 - 2 groups independently selected from halogen, OC_4 (sic), SO_2CH_3 , CF_3 , amino, alkyl or 3,4-dichloro, benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl or 9-fluorene;

$Z' = P(O)(OBn)_2, P(O)(OH)_2, (CH_2)_pC(O)NHOH, (CH_2)_pCOOH, SO_2CH_3, SO_2NH_2, CO(CH_2)_pCH(NH_2)COOH, COCH(NH_2)(CH_2)_pCOOH, CO_2CH_3, CONH_2, (CH_2)_pO(CH_2)_pCOOH, (CH_2)_pO(CH_2)_pCONHOH, (CH_2)_pNHSO_2CH_3, (CH_2)_pNHC(S)NHCH(COOH)(CH_2)_pCOOH, (CH_2)_pSO_3H, tetrazol-5-ylmethyl$ or a group of formula (i);

$Bn = CH_2$ -phenyl;

$p = 0-20$;

$R_3, R_4 = H$ or acyl;

$X_2 = COOH, NHSO_2CH_3, NHP(O)(OBn)_2, NHP(O)(OH)_2, OP(O)(OBn)_2$ or $OP(O)(OH)_2$;

$X, Y = CH_2NHSO_2CH_3, CH_2NHP(O)(OBn)_2, NHP(O)(OH)_2, CH_2OP(O)(OBn)_2, CH_2OP(O)(OH)_2, (CH_2)_qO(CH_2)_qCOOH, (CH_2)_qO(CH_2)_qSO_3H, (CH_2)_qO(CH_2)_qCHNHOH, CH_2NHC(S)NHCH(COOH)(CH_2)_qCOOH$ or a group of formula (ii);

$q, r = 1 - 20$; and

$X_3 = COOH, NHSO_2CH_3, NHP(O)(OBn)_2, NHP(O)(OH)_2, OP(O)(OBn)_2$ or $OP(O)(OH)_2$;

ACTIVITY - Analgesic; anti-**pruritic**.

MECHANISM OF ACTION - **Opioid kappa receptor agonist**.

(I) were tested against (3H)-diprenorphine binding to cloned human **kappa receptor**. Methyl 4-(2-glycyl-4-(trifluoromethylphenyl)acetyl)-3-(R,S)-((1-pyrrolidinyl)-methyl)-1-piperazinecarboxylate (Ia) had a K_i of 248 nM against (3H)-diprenorphine.

USE - Useful for preventing or treating **pruritis**.

ADVANTAGE - Unlike other treatments for **pruritis**, this therapy uses compounds with no activity within the central nervous system. Dependence and central nervous system side-effects are therefore avoided.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B05-B01J; B07-D11; B14-C01; B14-L01; B14-N17

L108 ANSWER 7 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2000-328360 [28] WPIX

CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]

DNC C2000-099459

TI New method for prevention or treatment of **pruritis** comprising administration of an arylacetamide compound which is a **kappa opioid agonist**..

DC B03

IN CHANG, A; GAUL, F; GUO, D; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 1

PI US 6054445 A 20000425 (200028)* 121p A61K031-675

ADT US 6054445 A Cont of US 1996-612680 19960308, Div ex US 1997-796078 19970205, Div ex US 1997-899086 19970723, CIP of US 1998-34661 19980303, CIP of US 1998-150369 19980909, Div ex US 1998-183011 19981030, US 1999-307387 19990507

FDT US 6054445 A Cont of US 5646151, Div ex US 5688955, Div ex US 5744458, CIP

of US 5945443

PRAI US 1998-183011 19981030; US 1996-612680 19960308; US 1997-796078 19970205; US 1997-899086 19970723; US 1998-34661 19980303; US 1998-150369 19980909; US 1999-307387 19990507

IC ICM A61K031-675
ICS A61K031-40

AB US 6054445 A UPAB: 20010822

NOVELTY - A new method for prevention or treatment of **pruritis** comprises administration of an arylacetamide compound (I) or its salt.

DETAILED DESCRIPTION - A new method for prevention or treatment of **pruritis** comprises administration of an arylacetamide compound of formula (I) or its salt.

n = 1-3;
R1, R2 = CH3; or
R1+R2 = -(CH2)m-, -CH2CH(OR)(CH2)2-, CH2CH(F)(CH2)2-, -(CH2)2O(CH2)2- or -(CH2)2CHCH2-;

m = 4-8;
R = H, 1-12C alkyl, acyl or aroyl;
Ar' = phenyl (mono- or di-substituted with halogen, OCH3, OH, SO2CH3, CF3, NH2, 1-12C alkyl, CN, optionally substituted sulfamoyl, -NH(CH2)uCO2R', -NH(CH2)u(CH=CH)u(CH2)CO2R', -NHCO(CH2)u(CH=CH)u(CH2)uCO2R', -NHP(O)(O-benzyl)2, -NHP(O)(OR')2, -(CH2)uNHSO2CH3, -(CH2)uNHC(S)NHCH(CO2R')(CH2)uCO2R', -CONHOH or -(CH2)uCONHOH), (NHC(O)CH((CH2)vX8))v'NHR6 or -OCH2C(O)R7;

u = 0-5;
R' = H or 1-4C alkyl;
R6 = H or acetyl;
X8 = -CO2H, -NHSO2CH3, -NHP(O)(O-benzyl)2, -NHP(O)(OH)2, -OP(O)(OBn)2 or -OP(O)(OH)2;
R7 = -NH(CH2)vCO2H, -NH(CH2)vCH(NH2)(CO2H), -NHCH(CO2H)(CH2)vNH2, -NH(CH2)vSO3H, -NH(CH2)vPO3H2, -NH(CH2)vNHC(NH)NH2 or -NHCH(CO2H)CH2)vCO2H;

v = 1-20;
X4, X5 = H, halo, OH, OCH3, CF3, NO2, NH2 (optionally substituted with acyl, carbamate, 1-12C alkyl or aryl sulfonates) or COR''; and
R'' = OH, amide, 1-12C alkoxy, aryloxy or heteroaryloxy.

ACTIVITY - **Antipruritic**.

MECHANISM OF ACTION - **Kappa opioid agonist**.

In an in vitro binding assay, (Z)-(+/-)-trans-((7-amino-2-(3,4-dichlorophenyl)-N-methyl-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphth-1-yl)acetamido)4-oxo-butenic acid had a Ki value of 28.0 nM for (3H)diprenorphine binding to the cloned human **kappa receptor**.

USE - (I) are useful for prevention or treatment of **pruritis** (claimed).

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B05-B01E; B05-B01F; B05-B01J; B05-B01K; B05-B01M; B05-B01N; B06-H; B07-H; B10-A08; B10-A09C; B10-A10; B10-A12C; B10-A13D; B10-A15; B10-A17; B10-A18; B10-B01; B10-B02B; B14-L01; B14-N17C

L108 ANSWER 8 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2000-316903 [27] WPIX

CR 1998-332207 [29]; 1999-131835 [11]; 1999-152855 [13]; 2000-072070 [06]; 2001-090169 [03]

DNC C2000-095770

TI Pharmaceutical treatment for **pruritis** in mammals involves administering compositions containing **kappa opioid receptor agonists**.

DC B03

IN CHANG, A; COWAN, A; FARRAR, J J; KUMAR, V; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 1

PI US 6048860 A 20000411 (200027)* 19p A61K031-495

ADT US 6048860 A Div ex US 1997-892599 19970714, Div ex US 1998-64695
19980422, Div ex US 1998-184393 19981102, US 1999-411111 19991004
FDT US 6048860 A Div ex US 5760023, Div ex US 5869521, Div ex US 6004964
PRAI US 1997-892599 19970714; US 1998-64695 19980422; US 1998-184393
19981102; US 1999-411111 19991004

IC ICM A61K031-495

ICS A61K031-445; A61K031-47; A61K031-50; A61K031-505

AB US 6048860 A UPAB: 20010220

NOVELTY - A method for treating **pruritis** in mammals by giving compositions comprising **kappa-opioid receptor agonists** (I) is new.

DETAILED DESCRIPTION - A new method for preventing and treating **pruritis** in mammals comprises the administration of a composition comprising **kappa-opioid receptor agonists** of formula (I) or its pharmaceutical salts.

R1, R2 = hydrogen (H), 3-6C alkenyl, 3-6C cycloalkyl or 4-12C cycloalkylalkyl; or

R1 + R2 = 2-8C polymethylene or 2-6C alkenylene either being optionally substituted with a heteroatom; or

NR1R2 = 5-membered ring (optionally containing an oxygen atom next to the nitrogen) or a 6-membered ring optionally containing 1 unsaturated unit optionally substituted with hydroxy, 1-6C acyloxy, oxo, methylene, COR10, OR11, NHR11 or N=NOR12;

R10, R12 = 1-6C alkyl;

R11 = H, 1-6C alkyl, aryl or aryl(1-6C alkyl); or

R3 = H, 1-6C alkyl or phenyl; or

R3 + R1 = -(CH2)3 or (CH2)4;

R4 = 1-6C alkyl or phenyl;

R5 = H; or

R4 + R5 = 2-5C linear polymethylene;

R6 = hydroxy, 1-6C alkyl, 1-6C hydroxyalkyl, 1-6C carboxyalkyl, phenyl, oxo, amino, carboxy, amido, optionally substituted methylene, COR13, COOR13, COCOR13 or NRxCORx;

R13 = H or optionally substituted 1-10C hydrocarbon;

Rx = 1-6C alkyl;

R6 + E = 5-6 membered ring with one or more heteroatoms;

R7 = H; or

R7+R6 = single or fused 5-12C aryl or 5-12C heterocyclyl containing up to 4 heteroatoms from oxygen, sulfur and nitrogen optionally substituted with H, 1-6C alkyl, CH2OR14, halo, hydroxy, 1-6C alkoxy, 1-6C alkoxycarbonyl, thiol, 1-6C alkylthio, OCOR15, NHCOR16, NHSO2R17 or CH2SO2NR18R19;

R14, R15, R16, R17, R18, R19 = H, 1-6C alkyl, aryl or aralkyl;

A = (hetero)aryl optionally mono- or disubstituted with 1-6C alkyl, 2-6C alkenyl, 1-6C haloalkyl, 2-6C haloalkenyl, 2-6C haloalkynyl, aryl, aralkyl, hydroxy, 1-6C alkoxy, 1-6C haloalkoxy, thiol, 1-6C alkylthio, 1-6C haloalkylthio, halo, nitro, cyano, carboxy, aryloxy, aralkoxycarbonyl, carbamoyl, sulfonyl or sulfamoyl;

E = methylene, sulfur, oxygen or imino;

R8 = H or 1-6C alkyl;

R9 = H; or

R9 + R8 = (CRaRa)m-C(=Y)-;

Ra = H or 1-6C alkyl (up to 3 alkyls);

m = 1-3; and

Y = O or 2 hydrogens.

ACTIVITY - Anti-**pruritic**; anti-hyperalgesic.

Swiss albino mice were subcutaneously injected with Compound 48/80 (RTM) (2 mg/ml) following a subcutaneously injected pre-treatment of **kappa agonist** (10 mg/kg) in Cremaphor EL. Irritation, as measured by observing rear lib **scratching** movement, was reduced by 85 % compared to untreated controls.

MECHANISM OF ACTION - Kappa opioid receptor agonist.

USE - Useful for treating **pruritis** in mammals including that caused by irritation, inflammation, local infection, acute skin injury, toothache, poison ivy, allergy and dermatitis.

ADVANTAGE - The method is more effective than antihistamine and

opiate anti-pruritic therapies.

Dwg.0/0

FS CPI
FA AB; GI; DCN
MC CPI: B06-H; B14-C01; B14-C03; B14-G02A; B14-N17

L108 ANSWER 9 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2000-194848 [17] WPIX

CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30];
1999-508187 [42]; 2000-022101 [54]; 2000-256918 [22]; 2000-328360 [27];
2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]

DNC C2000-060334

TI Substituted heteroaromatic benzyl **kappa opioid agonists** are used in the prevention or treatment of pururitis.

DC B03

IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 1

PI US 6028063 A 20000222 (200017)* 67p A61K031-675

ADT US 6028063 A CIP of US 1996-612680 19960308, CIP of US 1997-796078
19970205, Div ex US 1997-891833 19970714, Div ex US 1998-45522 19980321,
US 1999-307517 19990507

FDT US 6028063 A CIP of US 5646151, CIP of US 5688955, Div ex US 5763445

PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078
19970205; US 1998-45522 19980321; US 1999-307517 19990507

IC ICM A61K031-675

ICS A61K031-40

AB US 6028063 A UPAB: 20010822

NOVELTY - Prevention or treatment of pururitis comprises administration of substituted heteroaromatic benzyl derivatives (I)

DETAILED DESCRIPTION - Prevention or treatment of pururitis comprises administration of substituted heteroaromatic benzyl derivatives of formula (I).

n = 1-3;

R1, R2 = CH3; or

R1+R2 = (CH2)m, CH2CH(OH)(CH2)2, CH2CH(F)(CH2)2, (CH2)2O(CH2)2 or (CH2)2CH=CH(CH2)2;

m = 4-8;

Ar = 3,4-dichlorophenyl, phenyl optionally mono- or di-substituted with T', benzothiophenyl, benzofuranyl, naphthyl, diphenylmethyl, or 9-fluorene;

T' = halogen, OCH3, SO2CH3, CF3, NH3 or alkyl;

X7 = NHSO2CH3, NHP(=O)(OBn)2, NHP(=O)(OH)2, (CH2)uNHSO2CH3, (CH2)uNHC(=S)NHCH(CO2)(CH2)uCO2H, CONHOH, (CH2)uCONHOH, OCH2C(=O)R7 or a group of formula (a);

Bn = benzoyl;

u = 1-5;

R6 = H or acetyl;

X8 = CO2H, NHSO2CH3, NHP(=O)(OBn)2, NHP(=O)(OH)2, OP(=O)(OBn)2 or OP(=O)(OH)2;

R7 = NH(CH2)vCO2H, NH(CH2)vCH(NH2)CO2H, NHCH(CO2H)(CH2)vNH2,

NH(CH2)vSO3H, NH(CH2)vP(=O)(OH)2, NH(CH2)vNHC(NH)NH2 or

NHCH(CO2H)(CH2)vCO2H;

V = (CH2)v; and

v = 1-20.

ACTIVITY - Antipruritic.

Testing for antipruritic activity was carried using the mouse scratch model, the scratching induced by compound 40/80 (RTM). 1 Mouse out of groups of 8-10 was subjected to standard challenge with the test compound and the number of hindleg scratching movements measured. Over a range of dosages the mean values of scratching for each group of mice were normalized relative to % antagonism of scratching and plotted against dosage. The compounds tested showed dose-dependant antipruritic activity of 15-95% based on dosages of 0.5-10 mg/kg.

No specific compound biological data given.

MECHANISM OF ACTION - Kappa opioid

agonist.

USE - The compounds (I) are **kappa opioid agonists** used in the treatment of pruritis.

ADVANTAGE - **Kappa opioid agonists** are effective and have no central nervous system effects.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B07-D03; B07-D05; B07-D06; B14-C03; B14-N17

L108 ANSWER 10 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 2000-072070 [06] WPIX

CR 1998-332207 [29]; 1999-131835 [11]; 1999-152855 [13]; 2000-316903 [25]; 2001-090169 [03]

DNC C2000-020499

TI Treatment and prevention of **pruritis** comprises administration of sulfonamide or acetamide derivatives.

DC B05 B06

IN CHANG, A; COWAN, A; FARRAR, J J; KUMAR, V; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 1

PI US 6004964 A 19991221 (200006)* 20p A61K031-495

ADT US 6004964 A Div ex US 1997-892599 19970714, Div ex US 1998-64695 19980422, US 1998-184393 19981102

FDT US 6004964 A Div ex US 5760023, Div ex US 5869521

PRAI US 1997-892599 19970714; US 1998-64695 19980422; US 1998-184393 19981102

IC ICM A61K031-495

AB US 6004964 A UPAB: 20010220

NOVELTY - Treatment and prevention of **pruritis** comprises administration of sulfonamide or acetamide derivatives (I), or their salts.

DETAILED DESCRIPTION - Treatment and prevention of **pruritis** comprises administration of sulfonamide or acetamide derivatives of formula (I), or their salts.

n = 0-1;

R = phenyl (optionally substituted by 1-3 Q1), alkylamino, dialkylamino, amido, sulfonamido, carboxamido (optionally mono- or disubstituted), ureido (optionally mono- or disubstituted), or 1-7C alkyl or 3-7C cycloalkyl (both optionally substituted by Q2), or B'R7, or DR8;

Q1 = halo, 1-6C alkyl, OH, OCONH2, OCONHalkyl, OCON(alkyl)2, 1-6C alkoxy, CF3, 1-4C alkoxy(1-4C)alkoxy, carboxy(1-4C)alkoxy, CN, NO2 or NH2;

Q2 = OH, NH2, amidino, guanidino, aminocarbonyl, carboxy, 1-6C alkoxy, 1-6C alkylloxycarbonyl, 3-6C alkenyloxycarbonyl, 3-6C alkynyloxycarbonyl, 1-6C alkanoyloxy, 1-6C alkylsulfide, 1-6C alkylsulfoxide, 1-6C alkylsulfone, 1-6C alkylaminocarbonyl, 1-6C acylamino, 1-6C acylmethylamino or 1-6C alkylamino;

B' = CH2, CH(CH3) or a single bond;

R7 = 6-10C aryl (optionally substituted by 1-3 Q1), alkylamino, dialkylamino, amido, sulfonamido, carboxamido (optionally mono- or disubstituted), ureido (optionally mono- or disubstituted);

D = a bond, CH2, CH(CH3), CH2O, CH(CH3)O, CH2S, CH(CH3)S, CH2NH or CH(CH3)NH;

R8 = a 4-6 membered heterocyclyl containing 1-4 heteroatoms selected from O, S or N (optionally S-substituted by oxygen, optionally N-substituted by oxygen, OH or 1-3C alkyl, or optionally C-substituted by one or more Q3);

Q3 = NH2, OH, SH, CN, halo, 1-3C alkoxy, 1-3 alkylamino, 1-3C acylamino, 1-3C acylmethylamino or 1-3C alkylthio;

R1, R2 = H, 1-6C alkyl, 3-5C alkenyl, 3-5C alkynyl, or 4-7C cycloalkyl; or

NR1R2 = 1-azetidiny, 1-pyrrolidinyl (optionally 3-substituted by Q4), 1-piperazinyl (optionally 4-substituted by 1-3C alkyl), 1-morpholino, 2,5-dihydro-1H-pyrrolidin-1-yl, 3-azabicyclo(3.1.0)hexan-3-yl, or

3-azabicyclo(3.2.0)heptan-3-yl;

Q4 = OH, CH₂OH, tri(1-6C)alkylsilyloxy, acyloxy, 1-6C alkyl, 1-6C alkoxy, or 1-6C alkanoyloxy;

R3 = H, 1-7C alkyl, or benzyl or heterocyclyl (optionally substituted by 1-3 Q5), or mono-, di- or trihalomethyl, CN, COR₉, CH=NOR₁₀, OR₁₀, SR₁₀, CH₂CN, CH₂OR₁₀, CH₂SR₁₀, CH₂S(O)R₁₀, CH₂S(O)R₁₀, CH₂N(R₁₀)(R₁₁), CH₂(R₁₀)(R₁₁) (sic), CH₂N(R₁₀)OH, CH₂N(COR₁₀)OH, CH₂N(R₁₀)COR₁₁, CH₂N(R₁₀)S(O)R₁₁, or CH₂OCOR₁₀;

Q5 = halo, 1-4C alkyl, 1-4C alkoxy, or methoxycarbonyl;

R9 = H, OH, NH₂, NHOH, NHOCH₃, pyridylamino, NHN(CH₃)₂, 1-4C alkoxy, benzyloxy, 1-4C alkylamino, di(1-4C)alkylamino, 1-4C alkyl, or 1-4C alkylthio;

R₁₀, R₁₁ = H, 1-4C alkyl, 1-4C alkoxy, 7-11C phenylalkyl, or OR₁₂;

R₁₂ = H, 1-4C alkyl or a hydroxy protecting group;

X = CO or SO₂;

Y = a bond (where only one of R₄-R₆ is attached), C, OC, SC, S(O)C, S(O)C or CH₂C;

R₄-R₆ = H, OH, alkoxy, 1-4C alkylenedioxy, 1-8C alkyl, 3-8C cycloalkyl; phenyl, naphthyl, biphenyl, indanyl, 1-tetralone-6-yl, furyl, thienyl, pyridyl, thiazolyl, benzofuryl, or benzothienyl (all optionally substituted by 1-3 Q₆); or

R₅+R₆ = a group of formula (i);

Q₆ = halo, CN, OCONH₂, OCONHalkyl, OCON(alkyl)₂, OCOalkyl, NHCHO, NHCOalkyl, ureido, NHCONHalkyl, N(alkyl)CONHalkyl, NHCON(alkyl)₂, N(alkyl)CON(alkyl)₂, NHSO₂alkyl, COalkyl, CONH₂, CONHalkyl, CON(alkyl)₂, CH₂CONH₂, CH₂CONHalkyl, CH₂CON(alkyl)₂, OCH₂CONH₂, OCH₂CONHalkyl, OCH₂CON(alkyl)₂, 1-4C alkyl, 1-4C alkoxy, NH₂, OH, NO₂, CF₃, SO₂ alkyl, SOalkyl or mesyl;

R₁₃, R₁₄ = H, halo, OH, alkoxy, mono-, di- or trihalomethyl, NH₂, NHalkyl, N(alkyl)₂, NHCOalkyl, ureido, NO₂ or methylenedioxy; and

D' = CH₂, O, S, NH, CH₂CH₂, CH=CH, CH₂NH or CH₂N(alkyl).

ACTIVITY - **Antipruritic**; antihyperalgesic; antiinflammatory; dermatological; vulnerary.

Tests were performed in a mouse **scratch** model under blind conditions, using Swiss albino mice, to evaluate the **antipruritic** activity of (I). 3,4-Dichloro-N-methyl-N-(((1S)-1-(O-acetic acid-3-hydroxyphenyl)-2-(1-pyrrolidinyl)-ethyl)benzeneacetamide hydrochloride (Ia) gave 24, 72 and 85 % inhibition of **pruritis** at subcutaneous doses of 2.5, 5.0 and 10.0 mg/kg, respectively.

MECHANISM OF ACTION - **Kappa opioid agonists**.

USE - The method is used for the treatment and prevention of pruritis (claimed), such as that associated with irritation caused by inflammation following local infection, blisters, boils, or acute skin injuries (e.g. abrasions, superficial cuts or surgical incisions), toothaches, contusions, irritations, inflammatory skin conditions (e.g. poison ivy and allergic rashes), and dermatitis.

ADVANTAGE - The treatment is safe and effective.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B06-A01; B06-A03; B06-B01; B06-B02; B06-D13; B06-F05; B06-H; B07-A01; B07-B01; B07-D03; B07-D04C; B07-D11; B07-E03; B07-F01; B07-H; B08-D02; B08-D03; B10-A08; B10-A10; B10-A12C; B10-A17; B10-B01B; B14-C03; B14-N17

L108 ANSWER 11 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1998-347383 [30] WPIX

CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1999-508187 [42]; 2000-022101 [54]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27]; 2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]

DNC C1998-107342

TI Use of substituted piperazine derivatives which are **kappa opioid agonists** - for preventing or treating **pruritus**.

DC B02 B03

IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR, V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y

PA (ADOL-N) ADOLOR CORP

CYC 75

PI US 5763445 A 19980609 (199830)* 67p A61K031-495
 WO 9903468 A1 19990128 (199911) EN A61K031-40
 RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
 OA PT SD SE SZ UG ZW
 W: AL AU BA BB BG BR CA CN CU CZ EE GE GW HU ID IL IS JP KP KR LC LK
 LR LS LT LV MG MK MN MX NO NZ PL RO SG SI SK SL TR TT UA UZ VN YU
 ZA 9806208 A 19990331 (199918) 142p A61K000-00
 AU 9879801 A 19990210 (199925) A61K031-40
 NO 9906352 A 20000313 (200023) A61K000-00
 EP 998281 A1 20000510 (200027) EN A61K031-40
 R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
 BR 9810712 A 20000905 (200048) A61K031-40
 AU 725232 B 20001012 (200055) A61K031-40
 JP 2001510154 W 20010731 (200148) 208p A61K031-495
 KR 2001021853 A 20010315 (200159) A61K031-40
 NZ 500439 A 20011026 (200176) A61K031-40

ADT US 5763445 A CIP of US 1996-612680 19960308, CIP of US 1997-796078
 19970205, US 1997-891833 19970714; WO 9903468 A1 WO 1998-US12769 19980619;
 ZA 9806208 A ZA 1998-6208 19980713; AU 9879801 A AU 1998-79801 19980619;
 NO 9906352 A WO 1998-US12769 19980619, NO 1999-6352 19991220; EP 998281 A1
 EP 1998-930400 19980619, WO 1998-US12769 19980619; BR 9810712 A BR
 1998-10712 19980619, WO 1998-US12769 19980619; AU 725232 B AU 1998-79801
 19980619; JP 2001510154 W WO 1998-US12769 19980619, JP 2000-502767
 19980619; KR 2001021853 A KR 2000-700417 20000114; NZ 500439 A NZ
 1998-500439 19980619, WO 1998-US12769 19980619

FDT US 5763445 A CIP of US 5646151, CIP of US 5688955; AU 9879801 A Based on
 WO 9903468; EP 998281 A1 Based on WO 9903468; BR 9810712 A Based on WO
 9903468; AU 725232 B Previous Publ. AU 9879801, Based on WO 9903468; JP
 2001510154 W Based on WO 9903468; NZ 500439 A Div in NZ 513889, Based on
 WO 9903468

PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078
 19970205

IC ICM A61K000-00; A61K031-40; A61K031-495
 ICS A61K031-404; A61K031-405; A61K031-4439; A61K031-496; A61P017-04;
 C07D401-12

ICA C07D207-12; C07D241-04; C07D295-12; C07D403-06; C07D403-12

AB US 5763445 A UPAB: 20011227

A method for prevention or treatment of **pruritus** comprises
 administration of a substituted piperazine derivative of formula (I) in a
 carrier: n = 1-3; R1, R2 = CH3, or together are -(CH2)m,
 -CH2CH(OH)(CH2)2-, CH2CH(F)(CH2)2-, -(CH2)2O(CH2)2- or -(CH2)2CH=CHCH2-; m
 = 4-8; Ar = Ph optionally substituted with 1 or 2 halo, OMe, SO2Me, CF3,
 NH2, alkyl or 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl;
 diphenyl methyl; or 9-fluorenyl; Z = -P(O)(OBn)2, -P(O)(OH)2,
 -(CH2)pC(O)NHOH, -(CH2)pCO2H, -SO2Me, -SO2NH2, -CO(CH2)pCH(NH2)(CO2H),
 COCH(NH2)(CH2)pCO2H, -CO2Me, -CONH2, (CH2)pO(CH2)pCO2H,
 -(CH2)pO(CH2)pCONHOH, (CH2)pNHSO2Me, -(CH2)pNHC(S)NHCH(CO2H)(CH2)pCO2H,
 (CH2)pSO3H or a group of formula (i) or (ii): p = 0-20; R3 = H or Ac; X2,
 X3 = CO2H, -NHSO2Me, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or OP(O)(OH)2;
 X, Y = -CH2NHSO2Me, -CH2NHP(O)(OBn)2, -CH2NHP(O)(OH)2, CH2OP(O)(OBn)2,
 -CH2OP(O)(OH)2, -(CH2)qO(CH2)qCO2H, (CH2)qO(CH2)qSO3H,
 -(CH2)qO(CH2)qCHNHOH, CH2NHC(S)NHCH(CO2H)(CH2)qCO2H or a group of formula
 (iii): q, r = 1-20; R4 = H or Ac.

USE - (I) are **kappa opioid agonists**,
 useful as analgesics and for the treatment of **pruritus** (
 itch).

ADVANTAGE - (I) do not cause substantial central nervous system
 effects, and would not cause side effects associated with centrally acting
kappa opiate receptor agonists.

Dwg.0/0

FS CPI

FA AB; GI; DCN

MC CPI: B05-B01J; B05-B01M; B06-A01; B06-B01; B07-D03; B07-D05; B07-D11;
B07-D13; B07-E03; B14-C01; B14-G02A; B14-N17

L108 ANSWER 12 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1998-322462 [28] WPIX

DNC C1998-099185

TI Anti-pruritic agent - comprises an **opioid kappa-receptor agonist**, especially new morphinane quaternary ammonium salts and N-oxide compounds.

DC B02 B03

IN ENDOH, T; KAMEI, J; KAWAMURA, K; NAGASE, H; TANAKA, T; UTSUMI, J

PA (TORA) TORAY IND INC; (TORA) TORAY KK

CYC 26

PI WO 9823290 A1 19980604 (199828)* JA 92p A61K045-00

RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE

W: AU CA CN JP KR NO NZ US

AU 9749683 A 19980622 (199844)

NO 9803431 A 19980924 (199848) A61K031-40

EP 897726 A1 19990224 (199912) EN

R: AT BE CH DE DK ES FI FR GB GR IE IT LI NL PT SE

JP 10524506 X 19990608 (199933)

CN 1214634 A 19990421 (199934)

NZ 331001 A 20000526 (200033) A61K031-40

KR 99081978 A 19991115 (200052) A61K045-00

US 6174891 B1 20010116 (200106) A61K031-485

AU 738743 B 20010927 (200170) A61K045-00

US 6316461 B1 20011113 (200173) A61K031-485

ADT WO 9823290 A1 WO 1997-JP4267 19971121; AU 9749683 A AU 1997-49683 19971121; NO 9803431 A WO 1997-JP4267 19971121, NO 1998-3431 19980724; EP 897726 A1 EP 1997-912539 19971121, WO 1997-JP4267 19971121; JP 10524506 X WO 1997-JP4267 19971121, JP 1998-524506 19971121; CN 1214634 A CN 1997-193343 19971121; NZ 331001 A NZ 1997-331001 19971121, WO 1997-JP4267 19971121; KR 99081978 A WO 1997-JP4267 19971121, KR 1998-705696 19980724; US 6174891 B1 WO 1997-JP4267 19971121, US 1998-117052 19980824; AU 738743 B AU 1997-49683 19971121; US 6316461 B1 Div ex US 1998-117052 19980824, US 2000-615540 20000713

FDT AU 9749683 A Based on WO 9823290; EP 897726 A1 Based on WO 9823290; JP 10524506 X Based on WO 9823290; NZ 331001 A Based on WO 9823290; KR 99081978 A Based on WO 9823290; US 6174891 B1 Based on WO 9823290; AU 738743 B Previous Publ. AU 9749683, Based on WO 9823290; US 6316461 B1 Div ex US 6174891

PRAI JP 1996-313476 19961125

IC ICM A61K031-40; A61K031-485; A61K045-00

ICS A61K031-47; A61K031-54; C07D221-28; C07D279-12; C07D295-14;

C07D489-00; C07D489-100; C07D491-08

AB WO 9823290 A UPAB: 19980715

Antipruritic agent comprises an **opioid kappa-receptor agonist**. Also claimed are morphinane quaternary ammonium salt derivatives and morphinane N-oxide derivatives of formula (I): Q = O- or R6X-; R1 = 1-5C alkyl, 4-7C cycloalkylalkyl, 5-7C cycloalkenylalkyl, 7-13C aralkyl, 4-7C alkenyl or aryl; R2 = H, OH, NO2, 1-5C alkanoyloxy, 1-5C alkoxy or 1-5C alkyl; R3 = H, OH, 1-5C alkanoyloxy or 1-5C alkoxy; R4 = H, 1-5C alkyl or 6-12C aryl; A = 1-6C alkylene, CH=CH or C triple bond C; R5 = phenyl, naphthyl, furyl, benzofuryl or a group of formula (i)-(iii): all optionally substituted by Q. N.B. no bonding group is shown for any of R5. T = CH or O; l = 1-5; m+n = at most 5; Q = 1-5C alkyl, 1-5C alkoxy, 1-5C alkenoyloxy, OH, F, Cl, Br, I, NO2, CN, isothiocyanato, CF3, CF3O or methylenedioxy; R5 and X are not defined in the claims in the disclosure; R6 = 1-5C alkyl or aryl; and X = anion.

(I) are prepared by reacting a compound corresponding to (I; Q is absent) with R6X, CH3SO3R6 or a peracid.

USE - The agent including compounds (I) are useful for the treatment and prevention of **pruritus** including **pruritus** accompanying atopic dermatitis, neurodermatitis, contact dermatitis, dermatitis due to mites, age related skin disorders, insect bites, photosensitivity, blisters athlete's foot, psoriasis, internal

conditions (such as malignant tumours, liver disorders, diabetes, and renal insufficiency) and pregnancy. Dosage is 0.1 mg - 1000 mg/day orally or 0.001 mg/m²-10 mg/m² topically.

Dwg.0/1

FS CPI
FA AB; GI; DCN
MC CPI: B04-A04; B14-A04; B14-H01; B14-N17B; B14-N17C; B14-S04

L108 ANSWER 13 OF 14 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD

AN 1997-340994 [31] WPIX

DNC C1997-109521

TI New **opioid** peptide(s) which bind mu **receptors** specifically - have **agonist** or antagonist activity and are used for study and localisation of mu **receptors** and to treat peripheral side effects of morphine etc..

DC B04 D16

IN DOOLEY, C T; HOUGHTEN, R A

PA (TORR-N) TORREY PINES INST MOLECULAR STUDIES

CYC 1

PI US 5641861 A 19970624 (199731)* 92p A61K038-08

ADT US 5641861 A US 1995-487006 19950607

PRAI US 1995-487006 19950607

IC ICM A61K038-08

ICS A61K038-04

AB US 5641861 A UPAB: 19970731

Peptides of formulae (1)-(7), (214), (221) and (222) are new:

Ac-Phe-Arg-Trp-Trp-Tyr-X-NH₂ (1)

Ac-Arg-Trp-Ile-Gly-Trp-X-NH₂ (2)

Trp-Trp-Pro-Lys-His-X-NH₂ (3)

Trp-Trp-Pro-X1-NH₂ (4)

Tyr-Pro-Phe-Gly-Phe-X-NH₂ (5)

D-Ile-D-Met-D-Ser-D-Trp-D-Trp-(Gly)n-X2-NH₂ (6)

D-Ile-D-Met-D-Thr-D-Trp-Gly-X2-NH₂ (7)

Tyr-Al-B2-C3-NH₂ (214)

Pm and red (MexHy-Tyr-(NMe)z-Tyr-(X3)z-NH₂) (221)

Trp-Trp-Pro-D4-(His)z-(X)z-NH₂ (222)

X = any natural amino acid; X1 = Lys or Arg; n and z = 0 or 1; X2 = Gly or the D form of any naturally occurring amino acid; Al = D-norvaline or D-norleucine; B2 = Gly, Phe or Trp; C3 = Trp or naphthylalanine; x and y = 0-2, but not over 2 in total; X3 = Phe, DPhe or benzylamino; D4 = Lys or Arg; Pm and red indicate permethylation and reduction of all CO in peptide links to methylene.

USE - The new compounds are **opioids** specifically binding to the mu **receptor**. They are useful: (i) for in vitro assay and study of **opiate receptor** subtypes, particularly mu **receptors** in the brain; (ii) for in vivo localisation of **receptor** subtypes; and (iii) therapeutically to block the peripheral effects (e.g. constipation and **pruritus**) of centrally acting pain killers such as morphine.

ADVANTAGE - These compounds are very selective for the mu **receptor**, over binding to the delta and **kappa receptor** subtypes.

Dwg.0/7

FS CPI
FA AB; DCN
MC CPI: B04-C01A; B04-C01B; B04-N04A; B12-K04; B14-E09; B14-G02A; B14-L01; B14-L06; D05-H09

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AN 1997-051893 [05] WPIX

DNC C1997-017171

TI **Opioid** peptide(s) selective for **kappa-opiate receptor** - useful as analgesics, to treat **receptor** -associated pathologies and to diagnose **receptor** subtype.

DC B04 D16

IN DOOLEY, C T; HOUGHTEN, R A

PA (TORR-N) TORREY PINES INST MOLECULAR STUDIES
CYC 22
PI WO 9640206 A1 19961219 (199705)* EN 28p A61K038-07
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9660429 A 19961230 (199716) A61K038-07
US 5610271 A 19970311 (199716) 18p A61K038-07
EP 833652 A1 19980408 (199818) EN A61K038-07
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AU 699543 B 19981203 (199909) A61K038-07
JP 11512075 W 19991019 (200001) 19p C07K007-06
ADT WO 9640206 A1 WO 1996-US8871 19960603; AU 9660429 A AU 1996-60429
19960603; US 5610271 A US 1995-472219 19950607; EP 833652 A1 EP
1996-918080 19960603, WO 1996-US8871 19960603; AU 699543 B AU 1996-60429
19960603; JP 11512075 W WO 1996-US8871 19960603, JP 1997-501339 19960603
FDT AU 9660429 A Based on WO 9640206; EP 833652 A1 Based on WO 9640206; AU
699543 B Previous Publ. AU 9660429, Based on WO 9640206; JP 11512075 W
Based on WO 9640206
PRAI US 1995-472219 19950607
REP 2.Jnl.Ref; US 4261883; US 5017689; US 5338668
IC ICM A61K038-07; C07K007-06
ICS A61K031-00; A61K038-00; A61K038-08; C07K005-10; C07K005-103;
C07K005-107
AB WO 9640206 A UPAB: 19970129
Peptides of formulae Ac-A1-B2-C3-Arg-Tyr-Arg-Tyr-Arg-Arg-NH2 (I),
(D)Phe-D4-E5-F6 (II) and (D)Nle-D4-E5-F6 (III) are new, in which A1 = Tyr
or Arg, B2 = Arg or Phe, C3 = Thr, Phe or Met, D4 = (D)-naphthylalanine
(NapAla) or (D)Phe, E5 = (D)Nle, Trp or (D)Ile, and F6 = (D)Arg or
(D)-cyclohexylalanine (ChAla).
Peptides (I)-(III) are **opioid** peptides selective for the
Kappa (K) opiate receptor. The peptides which
act as **K-receptor agonists** are useful as analgesics,
while those which act as antagonists are useful for treating pathologies
associated with the **K-receptor**. For example, the peptides could
be used to block unwanted peripheral effects of centrally acting pain
killers (such as constipation and **pruritus** resulting from
morphine admin.). Also, the novel peptides are useful in-vitro to study
opiate receptor subtypes in brain and other tissues and
similarly in-vivo to localise **opioid receptor**
subtypes.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B04-C01A; B04-C01B; B14-C01; D05-H09
ABEQ US 5610271 A UPAB: 19970417
A peptide having the structure:
Ac-A1-B2-C3-Arg-Tyr-Arg-Tyr-Arg-Arg-NH2,
wherein A1 is Tyr or Arg;
B2 is Arg or Phe; and
C3 is Thr, Phe, or Met.
Dwg.0/0

=> d all abeq tech

L110 ANSWER 1 OF 1 WPIX COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2000-022101 [02] WPIX
CR 1997-362978 [33]; 1997-479836 [42]; 1998-271113 [24]; 1998-347383 [30];
1999-508187 [42]; 2000-194848 [17]; 2000-256918 [22]; 2000-328360 [27];
2000-349606 [29]; 2001-234235 [13]; 2001-440271 [38]
DNC C2000-005297
TI Prevention or treatment of **pruritus**.
DC B02 B03 D21
IN CHANG, A; DEHAVEN-HUDKINS, D L; FARRAR, J J; GAUL, F; KRUSE, L I; KUMAR,
V; MARELLA, M A; MAYCOCK, A L; ZHANG, W Y
PA (ADOL-N) ADOLOR CORP

CYC 1
 PI US 5981513 A 19991109 (200002)* 73p A61K031-40
 ADT US 5981513 A CIP of US 1996-612680 19960308, CIP of US 1997-796078
 19970205, Div ex US 1997-891833 19970714, US 1998-45522 19980321
 FDT US 5981513 A CIP of US 5646151, CIP of US 5688955, Div ex US 5763445
 PRAI US 1997-891833 19970714; US 1996-612680 19960308; US 1997-796078
 19970205; US 1998-45522 19980321
 IC ICM A61K031-40
 ICS C07D207-04
 AB US 5981513 A UPAB: 20010822
 NOVELTY - Prevention or treatment of **pruritus** comprises
 administering a tetrahydronaphthylacetamide derivative (I).
 DETAILED DESCRIPTION - Prevention or treatment of **pruritus**
 comprises administering a tetrahydronaphthylacetamide derivative of
 formula (I) or its salt in a carrier.
 n = 1-3;
 R1, R2 = Me, (CH2)m, CH2CH(OH)CH22, CH2CH(F)(CH2)2, (CH2)2O(CH2)2 or
 (CH2)2CH=CH2 (sic);
 Ar = phenyl (optionally substituted by 1 or 2 halo, OMe, SO2Me, CF3,
 amino, alkyl or 3,4-dichloro), benzothiophenyl, benzofuranyl, naphthyl,
 diphenylmethyl or 9-fluorenyl;
 X4, X5 = OP(O)(OBn)2, OP(O)(OH), CO2H, SO3H, SO3H (sic),
 O(CH2)nCO2H, NHSO3Me, CONH(CH2)sCO2H, SO2NH(CH2)sCO2H,
 CONHCH((CHt)X6)(CONHCH((CH2)tX6)CO2H, (NHCOCH((CH2)nX6))NHR5 or
 SO2(NHCO(CH2)tX6)NHR5;
 s = 1-5;
 t = 1-20;
 R5 = H or Ac;
 X6 = CO2H, NHSO2Me, NHP(O)(OBn)2, NHP(O)(OH)2, OP(O)(OBn)2 or
 OP(O)(OH)2.
 ACTIVITY - **Antipruritic**. In the late phase formalin test on
 Sprague Dawley rat paws 2-(7-((+/-)-trans-1-(N-3,4-dichlorophenylacetamido-
 N-methylamino)-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthoxy))acetic acid
 (Ia) at 300 mu g showed 44% inhibition of flinching.
 MECHANISM OF ACTION - **Opioid-Antagonist-Kappa**
 USE - For preventing or treating **pruritus**.
 Dwg.0/0
 FS CPI
 FA AB; DCN
 MC CPI: B05-B01M; B05-B01N; B07-D03; B07-D05; B07-D06; B10-A08; B10-A09B;
 B10-B04B; B14-G02A; B14-N17; D08-B09A

=> d his

(FILE 'HOME' ENTERED AT 08:32:02 ON 18 JAN 2002)
 SET COST OFF

FILE 'HCAPLUS' ENTERED AT 08:32:19 ON 18 JAN 2002

L1 112 S E3,E5,E12-E14
 E KRUSE L/AU
 L2 185 S E3,E5-E9
 E CHANG A/AU
 L3 22 S E118
 E DEHAVEN/AU
 L4 16 S E9-E11
 L5 48 S E15-E18
 E HUDKINS/AU
 L6 1 S E4
 E GAUL F/AU
 L7 16 S E3-E5
 E KUMAR V/AU
 L8 772 S E3-E74
 E KUMAR VIRENDRA/AU
 L9 95 S E3
 L10 7 S E2

L11 1 S E5
E MARELLA M/AU
L12 24 S E3,E5,E6
E MAYCOCK A/AU
L13 64 S E3,E4,E6,E8,E9
E ZHANG W/AU
L14 554 S E3,E22
E ZHANG WEI/AU
L15 1248 S E3,E69
E ZHANG WEIYUAN/AU
L16 23 S E3
L17 3122 S L1-L16
E PRURIT/CW
L18 889 S E5,E6
E ANTIPRURIT/CW
E ITCH/CW
E PRURIGO/CW
E HYPERALG/CW
L19 327 S E4
E PRURITIS/CT
E E4+ALL
L20 890 S E5,E4+NT
E HYPERALG/CT
E E4+ALL
L21 1152 S E1,E2
E PRURIT
L22 1629 S E5-E21
E PRURIG
L23 74 S E4-E8
E ITCH
L24 1292 S E3,E6,E9,E10,E15,E16,E17,E22
E SCRATCH
L25 16643 S E3,E5,E10,E13-24
L26 8 S E24,E26,E34
L27 29 S E38
L28 1 S E37
E ANTIITCH
L29 67 S E4
E ANTIPRUR
L30 274 S E5-E12
L31 2 S E93
L32 1 S E103
E ANTISCRATCH
L33 129 S E3,E4,E5
E ANTIHYPERALG
L34 110 S E4-E6
L35 20532 S L18-L34
L36 2743 S KAPPA(L)RECEPTOR(L)AGONIST(L) (OPIOID? OR OPIAT?)
L37 4877 S KAPPA(L)RECEPTOR(L) (OPIOID? OR OPIAT?)
L38 31 S L35 AND L36
L39 46 S L35 AND L37
L40 115 S (OPIOID? OR OPIAT?) (L)AGONIST AND L35
L41 235 S (OPIOID? OR OPIAT?) (L)RECEPTOR AND L35
L42 57 S (OPIOID? OR OPIAT?) (L)KAPPA AND L35
L43 57 S L38,L39,L42
L44 200 S L40,L41 NOT L43
L45 41 S KAPPA(L)AGONIST AND L35
L46 58 S L43,L45
L47 200 S L40,L41 NOT L46
L48 5 S L17 AND L46
L49 1 S L17 AND L47
L50 6 S L48,L49
E ADOLOR/PA,CS
L51 30 S E3-E14
L52 14 S L51 AND L35
L53 9 S L51 AND L36,L37

L54 17 S L51 AND (OPIOID? OR OPIAT?) (L) (AGONIST OR RECEPTOR OR KAPPA
 L55 13 S L51 AND KAPPA (L) AGONIST
 L56 7 S L53,L54 AND L52
 L57 7 S L50,L56
 L58 17 S L52-L55 NOT L57
 L59 251 S L46,L47 NOT L57,L58
 L60 110 S L59 AND (PY<=1996 OR PRY<=1996 OR AY<=1996)
 L61 18 S L60 AND (PERIPHERAL OPIATE RECEPTOR OR ANTIPRUR? OR SCRATCHIN
 L62 42 S L57,L58,L61
 L63 16 S L60 AND PRURITUS/CW,BI
 L64 50 S L62,L63

FILE 'HCAPLUS' ENTERED AT 09:08:46 ON 18 JAN 2002

FILE 'EMBASE' ENTERED AT 09:09:18 ON 18 JAN 2002

E PRURITIS/CT
 L65 15299 S (PRURITUS+NT OR PRURIGO OR HYPERALGESIA)/CT
 L66 19567 S PRURITIS OR PRURITUS OR PRURIGO OR ITCH OR ITCHING OR ITCHED
 E PRURIT
 L67 1771 S E6-E24
 L68 13458 S E25-E30,E33,E34
 E PRURIGO
 L69 751 S E3-E5
 E ITCH
 L70 3379 S E3,E7-E12
 L71 407 S E14
 E SCRATCH
 L72 2934 S E3,E7-E14,E16,E20-E23
 E HYPERALGES
 E HYPERALGAES
 L73 3610 S E4-E12
 L74 69 S E13-E24
 E ANTIPRURI
 L75 298 S E1,E2,E4-E15
 E ANTIITCH
 L76 3 S E3,E4
 E ANTISCRATCH
 L77 23430 S L65-L76
 L78 490 S KAPPA OPIATE RECEPTOR AGONIST+NT/CT
 L79 17 S L77 AND L78
 L80 1646 S L77 AND (OPIAT? OR OPIOID?)
 L81 364 S L80 AND AGONIST
 L82 774 S L80 AND RECEPTOR
 L83 134 S L80 AND KAPPA
 L84 430 S L81-L83 AND PY<=1996
 L85 0 S L79 AND L84
 L86 174 S L84 AND L81
 L87 130 S L86 AND L82
 L88 49 S L87 AND L83
 L89 7 S L88 AND (?PRURIT? OR ?PRURIG? OR ?ITCH? OR ?SCRATCH?)
 L90 1 S L89 AND FACIAL SCRATCHING

FILE 'EMBASE' ENTERED AT 09:58:14 ON 18 JAN 2002

FILE 'WPIX' ENTERED AT 09:58:23 ON 18 JAN 2002

E PURUIT
 E PRURIT
 L91 865 S E5-E16,E18,E19
 E PRURIG
 L92 80 S E4-E9
 E ITCH
 L93 1464 S E3-E6,E8-E13
 E SCRATCH
 L94 15946 S E2-E5,E10-E24,E29,E30,E31,E32
 E ANTIPRUR
 L95 527 S E4-E14

L96 E ANTIITCH
 1 S E3
 E ANTISCRATCH
 L97 161 S E3,E4
 L98 1397 S SKIN(L) (TINGL? OR ITCH? OR PRURIT? OR PRURIGO? OR SCRATCH?)
 L99 18521 S L91-L98
 L100 50 S L99 AND (OPIOID? OR OPIAT?)
 L101 18 S L100 AND KAPPA
 L102 21 S L100 AND AGONIST
 L103 35 S L100 AND RECEPTOR
 L104 17 S L101 AND L102,L103
 L105 18 S L102 AND L103
 L106 24 S L104,L105
 L107 17 S L106 AND L101
 L108 14 S L102 AND L107

FILE 'WPIX' ENTERED AT 10:06:16 ON 18 JAN 2002

FILE 'WPIX' ENTERED AT 10:14:53 ON 18 JAN 2002

L109 10 S L106 NOT L108
 L110 1 S L101 NOT L102-L109